Synthesis and Comparative Molecular Field Analysis (CoMFA) of Symmetric and Nonsymmetric Cyclic Sulfamide HIV-1 Protease Inhibitors

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We have previously reported on the unexpected flipped conformation in the cyclic sulfamide class of inhibitors. An attempt to induce a symmetric binding conformation by introducing P2/P2′ substituents foreseen to bind preferentially in the S2/S2′ subsite was unsuccessful. On the basis of the flipped conformation we anticipated that nonsymmetric sulfamide inhibitors, with P2/P2′ side chains modified individually for the S1′ and S2 subsites, should be more potent than the corresponding symmetric analogues. To test this hypothesis, a set of 18 cyclic sulfamide inhibitors (11 nonsymmetric and 7 symmetric) with different P2/P2′ substituents was prepared and evaluated in an enzyme assay. To rationalize the structure−activity relationship (SAR) and enable the alignment of the nonsymmetric inhibitors, i.e., which of the P2/P2′ substituents of the nonsymmetric inhibitors interact with which subsite, a CoMFA study was performed. The CoMFA model, constructed from the 18 inhibitors in this study along with seven inhibitors from previous work by our group, has successfully been used to rationalize the SAR of the cyclic sulfamide inhibitors. Furthermore, from the information presented herein, the SAR of the cyclic sulfamide class of inhibitors seems to differ from the SAR of the related cyclic urea inhibitors reported by DuPont and DuPont-Merck.

Introduction

The viral HIV-1 protease plays an important role in the maturation and production of infectious viral particles.[1] The protease has become an ideal target for the development of anti-HIV drugs, and five protease inhibitors have been approved by the FDA.[2] The protease inhibitors are capable of reducing the viral load in monotherapy but are usually administered in combination with reverse transcriptase inhibitors.[3] Treatment with these drugs will eventually lead to the development of resistant variants with a reduced sensitivity toward the inhibitors.[4] The emergence of mutant forms under the selective pressure of anti-HIV drugs suggests that new chemical entities with unique resistance profiles are urgently needed.

We previously prepared the carbohydrate based cyclic urea **1** and cyclic sulfamide **2**, which are potent HIV-1 protease inhibitors (Figure 1).[5] When compound **1** was cocrystallized with HIV-1 protease, a symmetric binding conformation similar to the related cyclic urea inhibitors reported by Lam et al.[6] was observed. The sulfamide **2**, however, adopted an unexpected flipped conformation placing the P1′ group in the S2′ pocket and the P2′ group in the S1′ pocket (Figure 1).[7] To study if a symmetric conformation of the sulfamide inhibitors could be induced we synthesized a series of inhibitors with P2/P2′ substituents foreseen to bind preferentially to the S2/S2′ subsites.[8] Since fewer hydrogen bond interactions seem to be available in S1/S1′ as compared to S2/S2′ ,[9,10] we anticipated that **3** should adopt a urea-type conformation. X-ray crystallographic studies, however, showed that **3** adopted a flipped conformation placing one of the polar P2/P2′ aryl ketoxime substituents in the largely lipophilic S1′ subsite (Figure 1).[8] We therefore expected that nonsymmetric sulfamide inhibitors, with P2/P2′ side chains modified individually for the S1′ and S2 subsites, should be more potent than the corresponding symmetric analogues.

We herein describe the synthesis and structure−activity relationship (SAR) of a series of symmetric and nonsymmetric carbohydrate derived cyclic sulfamide inhibitors. To explore the unique binding mode of the cyclic sulfamide class of inhibitors, the individual compounds of the series were chosen so that size, polarity, and hydrogen bonding capacity were varied. We also report on a conformational analysis study of the inhibitors inside the HIV protease and on a CoMFA study performed in order to rationalize the SAR and enable the alignment of the nonsymmetric inhibitors; i.e., which of the P2/P2′ substituents of the nonsymmetric inhibitors interact with which subsite.

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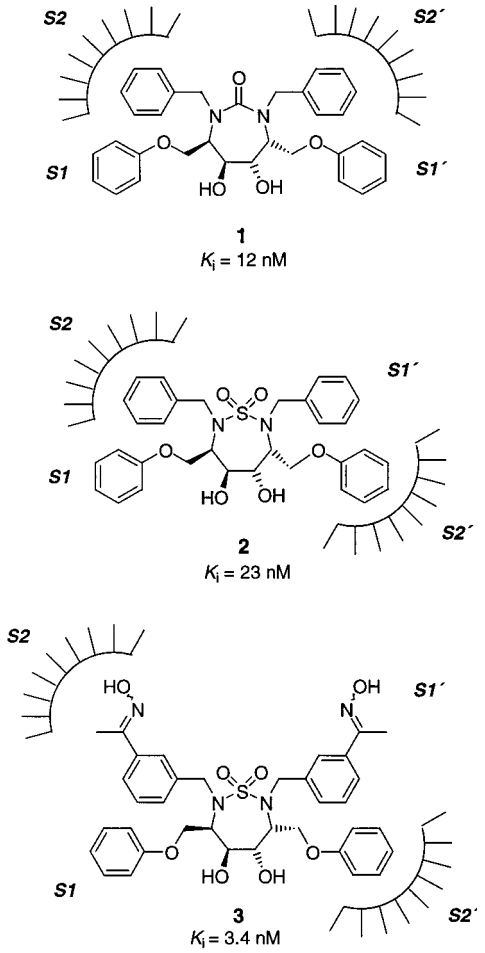


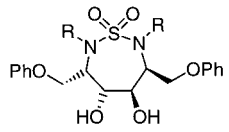
Figure 1. Structure of a cyclic urea inhibitor **1** with symmetric binding to HIV-1 protease and two cyclic sulfamide inhibitors **2** and **3** with nonsymmetric binding to HIV-1 protease.

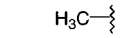
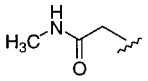
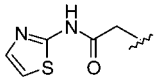
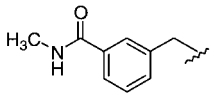
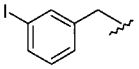
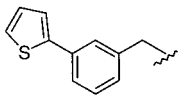
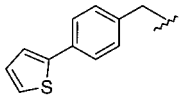
Methods

Inhibitor Design. To explore the SAR of the cyclic sulfamides, we synthesized a set of symmetric and a set of nonsymmetric analogues. The first set consisted of seven symmetrically substituted compounds with substituents chosen so that size and polarity varied (Table 1). We included substituents that had previously been shown to produce active protease inhibitors.[11,12] For example, thiazolyl heterocycles have been successfully employed in several inhibitors including the cyclic urea inhibitor XV638[13] and ritonavir.[14] Thienyl substitution in the P1/P1′ side chains of linear HIV-1 protease inhibitors was recently presented by our group.[15] These inhibitors, among other heteroaryl substituted compounds, exhibited high activity both in enzyme and cell assays. From preliminary modeling of the sulfamide compounds against the linear thienyl extended inhibitors, it was not clear whether the thienyl groups should be attached to the *meta* or the *para* position of the P2/P2′ phenyl rings so we synthesized both.

The second set of compounds encompassed 11 nonsymmetrically P2/P2′ substituted sulfamides (Table 2). In the first six of these compounds, we kept one of the P2/P2′ side chains constant (benzyl) and varied the other side chain using essentially the same substituents as for the symmetric inhibitors (Table 1). The final five compounds in Table 2 were in principle constructed from combinations of the substituents in Table 1. For comparison and development of CoMFA models, we also included a set of seven symmetrically substituted sulfamides previously synthesized in our laboratory (Table 3).

Table 1. Inhibitory Activities of Symmetric Cyclic Sulfamide Inhibitors



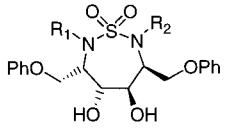
compd	R	K_i (nM)	pK_i[a] obsd	pK_i[a] calcd[b]
4		710	6.15	6.04
5		25 000	4.60	4.73
6		2200	5.66	5.93
7		39	7.41	7.43
8		93	7.03	7.27
9		2 200	5.66	5.72
10		920	6.04	6.14

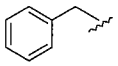
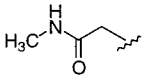
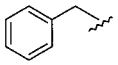
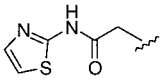
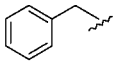
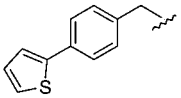
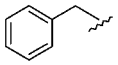
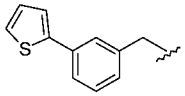
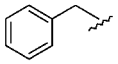
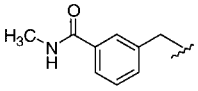
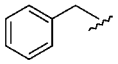
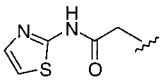
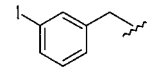
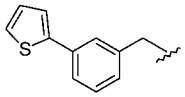
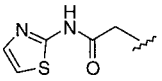
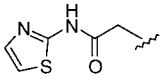
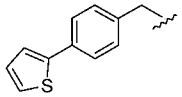
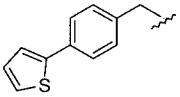
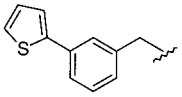
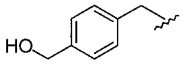
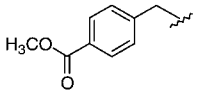
[a] −log K_i. [b] Based on the CoMFA model of all 25 inhibitors.

The S1/S1′ subsites of HIV-1 protease have been described as essentially lipophilic.[9,10] This is also true for the S2/S2′ subsites except toward the entrance to the active site where Asp29/29′, Asp30/30′, and Gly48/48′ are situated.[9,10] In the preliminary molecular modeling of these compounds, we hypothesized that the more polar P2 or P2′ substituent should interact with the S2 subsite rather than the S1′ subsite. A general trend seen in the preliminary molecular modeling of the inhibitors in the protease was that the S2/S2′ subsites were more prone than the S1/S1′ subsites to participate in hydrogen bonding.

Synthesis. Reduction of compound **27**[5] and subsequent cyclization with sulfamide[16,17] at 120 °C provided the cyclic sulfamide **28** in 53% yield. To take full advantage of the nonsymmetric binding conformation of the sulfamide scaffold we desired nonsymmetric inhibitors. Alkylation of the sulfamide nitrogens allows for the introduction of various substituents at one of the nitrogen atoms. High dilution and slow addition of the alkylating agent (Scheme 1) furnished, on average, 50% of the monosubstituted products (**29**−**31**), 15% of the

Table 2. Inhibitory Activities of Nonsymmetric Cyclic Sulfamide Inhibitors



compd	R_1(S2)	R_2(S1')	K_i (nM)	pK_i[a] obsd	pK_i[a] calcd[b]
11			510	6.29	6.40
12			1 400	5.85	5.56
13			350	6.46	6.65
14			63	7.20	6.94
15			86	7.07	7.43
16			11	7.96	8.11
17			510	6.29	6.09
18			140	6.85	6.89
19			1 800	5.75	5.85
20			6 000	5.22	5.18
21			7.3	8.14	8.04

Assignment of R1 and R2 groups are based on the alignment derived from the CoMFA model. [a] $-\log K_i$. [b] Based on the CoMFA model of all 25 inhibitors.

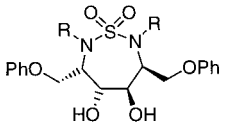
disubstituted products (**32**−**34**), and 15% of unreacted starting material (**28**) which was easily separable by flash chromatography.

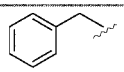
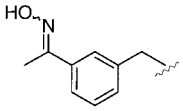
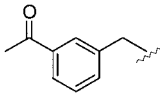
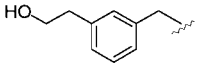
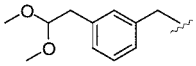
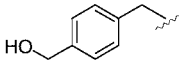
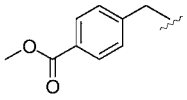
Alkylation of the cyclic sulfamide **28** with methyliodide, methylbromoacetate, methyl-3-bromomethylbenzoate, 3-iodobenzylbromide, and 4-bromobenzylbromide provided the symmetric compounds **36**−**38**, **32**, and **33**, respectively (Scheme 2). The synthesis of the nonsymmetric compounds **39**−**42**, starting from the monobenzyl compound **31** using methylbromoacetate, methyl 3-bromomethylbenzoate, 4-bromobenzylbromide, and 3-iodobenzylbromide as alkylating agents proceeded without difficulties. The nonsymmetric 3-bromobenzyl and 4-bromobenzyl compound (**42**) was synthesized from **29** in 85% yield. Hydrolysis with an aqueous solution of NaOH in THF smoothly converted the ester groups of **37**−**40** into the corresponding carboxylic acids. Using a peptide coupling reagent (HATU or PyBop) and a primary amine (methylamine or 2-aminothiazole) provided after deketalization compounds **5**−**7**, **12**, **13**, and **16**.

The dimethyl substituted inhibitor **4** was prepared in 77% yield via the alkylation of compound **28** with methyl iodide followed by hydrolysis. The Mitsunobu reaction[18,19] provided after hydrolysis inhibitor **11** from **31** in 65% yield.

The extension of the P2′ side chain with a 2-thienyl substituent was accomplished with the Suzuki reaction,[20,21] employing 2-thienylboronic acid as coupling reagent (Scheme 2). Instead of using standard heating with an oil bath, flash heating with a single mode microwave cavity was applied[22,23] which allowed for full conversion after 4 min at 45 W. Using this procedure and a subsequent hydrolysis step, compounds **32**, **33**, **40**, **41**, and **42** were converted into the inhibitors **9**, **10**,

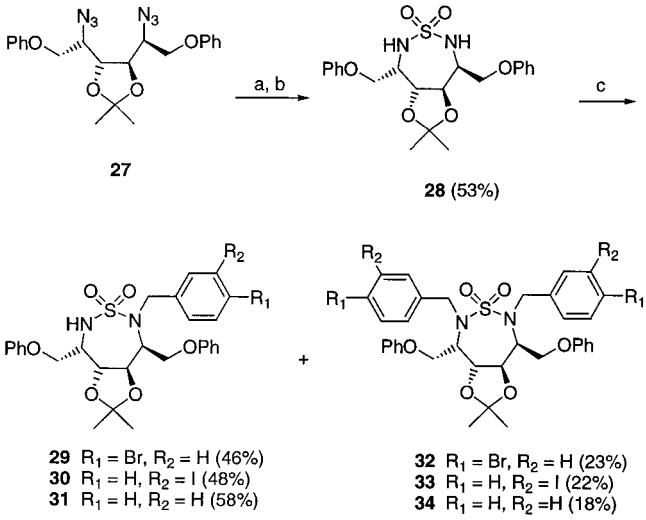
Table 3. Inhibitory Activities of Previously Reported Symmetric Cyclic Sulfamide Inhibitors



compd	R	K_i (nM)	pK_i[a] obsd	pK_i[a] calcd[b]
2		23	7.64	7.44
3		3.4	8.47	7.82
22		59	7.23	7.48
23		43	7.37	7.39
24		540	6.27	5.89
25		3.1	8.51	8.43
26		84	7.08	7.31

[a] $-\log K_i$. [b] Based on the CoMFA model of all 25 inhibitors.

Scheme 1[a]



[a] (a) H_2, Pd/C; (b) sulfamide, pyridine 120 °C; (c) benzylbromide, 4-bromo- or 3-iodobenzylbromide, DMF, K_2CO_3.

14, **15**, and **20**. Hydrolysis of the intermediate **34** furnished inhibitor **8** in 91% yield.

Synthesis of the bis-functionalyzed, nonsymmetric inhibitors **17**, **19**, and **18** started with the alkylation of the monosubstituted compounds **29** and **30** with methyl bromoacetate and provided **43**−**44** in 90% and 85% yields, respectively (Scheme 3). Saponification of the methyl ester groups of **43**−**44** followed by amide bond formation with 2-aminothiazole gave **45**−**46** in 47% and 69% yields, respectively. Using the microwave assisted Suzuki coupling and a subsequent deprotection step, compounds **45**−**46** were smoothly converted into the inhibitors **19** and **18**, delivering 53% and 49% yields, respectively. Hydrolysis of the intermediate **46** furnished inhibitor **17** in 92% yield.

HIV Protease Inhibition. HIV-1 protease was cloned and heterologously expressed in *Esherichia coli* and purified as described elsewhere.[24] The K_i values for the synthesized compounds were determined by a fluorometric assay[24] (Tables 1 and 2).

Crystallography. The details of the crystallization and structure determinations will be published elsewhere. Briefly, the complexes of HIV-1 protease, **21** (Figure 2a) and **16** (Figure 2b), were crystallized in space group $P2_12_12$ and determined to 1.8 and 1.9 Å resolution, respectively.

Conformational Analysis. The common core of the 25 inhibitors (where P2 and P2′ were truncated to methyl) was taken from the X-ray coordinates of the complex of **21** and HIV-1 protease (Figure 2a). The 11 asymmetric inhibitors were modeled in both possible binding modes to make a total of 36 structures.

Prior to conformational search, the compounds were subjected to substructure energy minimization in the active site of the protease. Calculations were performed under the AMBER*[25] force field with a GB/SA[26] solvation model in MacroModel 5.5.[27] The P2/P2′ groups were allowed to relax in a 6 Å shell from the **21**−HIV-1 protease complex (extended to full residues). The active site and the common core of the inhibitors were held fixed with a force constant of 100 kcal/mol Å^2.

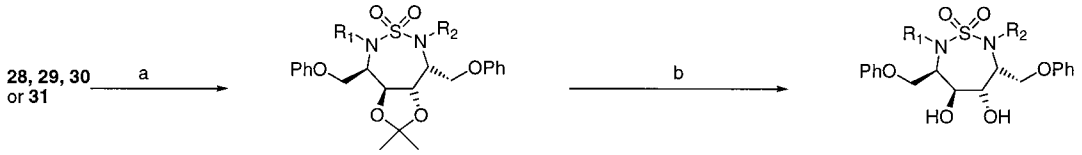
The conformational preferences of the P2 and P2′ groups of each minimized inhibitor was explored with 2000-step Monte Carlo runs in the environment described above. The P2/P2′ groups of the inhibitors contained 0 to 12 rotatable bonds. The lowest energy conformer of each compound was used for deriving the CoMFA models.

CoMFA Calculations. Sybyl[28] was used for all CoMFA (comparative molecular field analysis),[29] PLS (partial least squares),[30] and SAMPLS (sample-distance partial least squares)[31] calculations. Default settings were used for all calculations unless otherwise stated.

To minimize the number of points used for grid calculations in CoMFA, **21** was rotated to a standard frame of reference with the ORIENT BEST_VIEW command in Sybyl. All other inhibitors were fit by their common seven-membered ring to this frame of reference. MOPAC AM1[32] charges were assigned to all compounds.

An sp^3 carbon probe of +1 charge was used for grid calculations. The lattice was automatically generated with the default 4 Å padding to result in a box of approximately 30 × 19 × 15. Lattice generation was repeated after splitting the data into training and test sets, but the box remained approximately the same size. Cutoffs were set to the standard 30 kcal/mol except that electrostatics were dropped for each row where the steric cutoff was reached. Electrostatic contributions were calculated with a distance dependent dielectric (1/*r*). No smoothing functions were applied. Grid spacing was set to 2 Å. Standard CoMFA scaling was used for all PLS calculations.

Scheme 2[a]

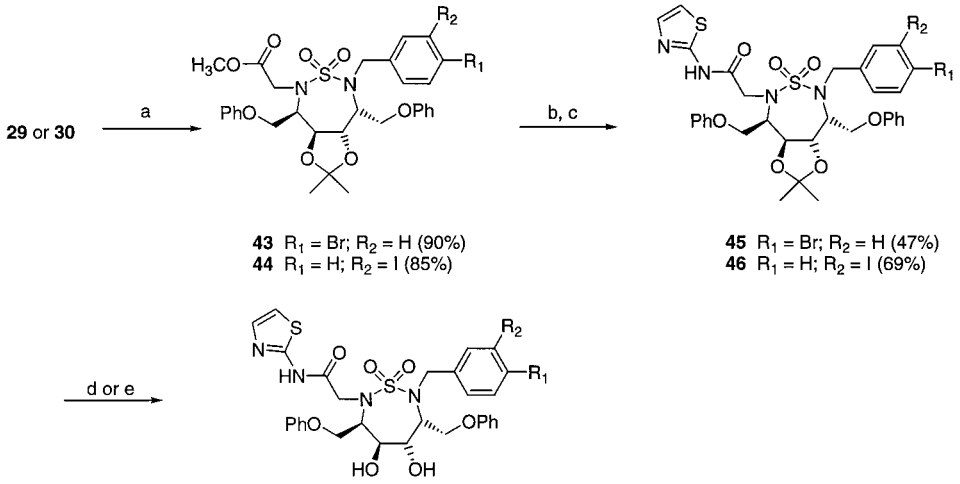


35 R_1= Methyl R_2= Methyl (84%)
36 R_1= Methoxycarbonylmethyl
R_2= Methoxycarbonylmethyl (82%)
37 R_1= 3-(Methoxycarbonyl)benzyl
R_2= 3-(Methoxycarbonyl)benzyl (79%)
38 R_1= 2-Methoxycarbonylmethyl R_2= Benzyl (91%)
39 R_1= 3-(Methoxycarbonyl)benzyl R_2= Benzyl (74%)
40 R_1= 4-Bromobenzyl R_2= Benzyl (75%)
41 R_1= 3-Iodobenzyl R_2= Benzyl (97%)
42 R_1= 3-Bromobenzyl R_2= 4-Bromobenzyl (85%)
32 R_1= 4-Bromobenzyl R_2= 4-Bromobenzyl (66%)
33 R_1= 3-Iodobenzyl R_2= 3-Iodobenzyl (85%)

4 R_1= Methyl R_2= Methyl (77%)
5 R_1= N-(Methylcarbamoyl)methyl
R_2= N-(Methylcarbamoyl)methyl (35%)
6 R_1= (N-2-Thiazolylcarbamoyl)methyl
R_2= (N-2-Thiazolylcarbamoyl)methyl (64%)
7 R_1= 3-(N-Methylcarbamoyl)benzyl
R_2= 3-(N-Methylcarbamoyl)benzyl (60%)
11 R_1= Methyl R_2= Benzyl (65%)
12 R_1= (N-Methylcarbamoyl)methyl R_2= Benzyl (35%)
13 R_1= (N-2-Thiazolylcarbamoyl)methyl R_2= Benzyl (38%)
16 R_1= 3-(N-methylcarbamoyl)benzyl R_2= Benzyl (48%)
14 R_1= 4-(2-thienyl)benzyl R_2= Benzyl (63%)
15 R_1= 3-(2-thienyl)benzyl R_2= Benzyl (73%)
20 R_1= 3-(2-thienyl)benzyl R_2= 4-(2-thienyl)benzyl (48%)
8 R_1= 3-Iodobenzyl R_2= 3-Iodobenzyl(91%)
10 R_1= 4-(2-thienyl)benzyl R_2= 4-(2-thienyl)benzyl (56%)
9 R_1= 3-(2-thienyl)benzyl R_2= 3-(2-thienyl)benzyl (65%)
21 R_1= 4-(hydroxymethyl)benzyl
R_2= 4-(methoxycarbonyl)benzyl (26%)

[a] (a) For **35**: methyliodide. For **36**, **38**: methylbromoacetate. For **37**, **39**: methyl-3-bromomethyl benzoate. For **33**, **40**: 4-bromobenzylbromide. For **42**: 3-bromobenzylbromide. For **32**, **41**: 3-iodobenzylbromide, DMF, K_2CO_3. (b) For **5**, **6**, **7**, **12**, **13**, **16**: (*i*) 2 M NaOH(aq); (*ii*) methylamin or 2-thiazolylamine, HATU, and DIEA; (*iii*) HCl/ether and methanol. For **4**, **8**, **11**: HCl/ether and methanol. For **9**, **10**, **14**, **15**, **20**: (*i*) 2-thienylboronic acid, $Pd(PPh_3)_4$; (*ii*) HCl/ether and methanol. For **21**: $LiBH_4$, ether.

Scheme 3[a]



43 R_1 = Br; R_2 = H (90%)
44 R_1 = H; R_2 = I (85%)

45 R_1 = Br; R_2 = H (47%)
46 R_1 = H; R_2 = I (69%)

17 R_1 = H; R_2 = I (92%)
19 R_1 = 2-Thienyl; R_2 = H (53%)
18 R_1 = H; R_2 =2-Thienyl (49%)

[a] (a) Methylbromoacetate, DMF, K_2CO_3; (b) 2 M NaOH(aq); (c) 2-aminothiazole, HATU; (d) for **17**: HCl/ether and methanol; (e) for **18**, **19**: (*i*) 2-thienylboronic acid, $Pd(PPh_3)_4$; (*ii*) HCl/ether and methanol.

SAMPLS with leave-one-out validation, no column filtering, and a maximum of six components was used for all cross-validation calculations to determine the q^2 (cross-validated correlation coefficient) and standard error of prediction. The optimal number of components for each model was determined by the minimum standard error of prediction. Final models were calculated with PLS without SAMPLS and cross-validation.

Determination of Binding Modes. Uncertainty over the binding mode of the 11 nonsymmetrical inhibitors, i.e., which of the P2 substituents interact with the S1/S1′ subsite, prompted us to generate CoMFA models for each of the 2048 (2^{11}) possibilities. Other central-ring conformations were not explored. The 10 fields available in the Advanced CoMFA module of Sybyl (standard, indicator, and parabolic and the steric or electrostatic components thereof and hydrogen bonding) were used in the calculations for a total of 20 480 models.

Discussion

Symmetric Inhibitors. Replacing the benzylic P2/P2′ side chains of **2** (K_i = 23 nM) with methyl groups led to inhibitor **4** with K_i = 710 nM. The lower activity of **4** can probably be attributed to a substantial reduction of favorable hydrophobic interactions with the protease. Interestingly, this 35-fold reduction in activity should be compared to the 500-fold reduction in activity

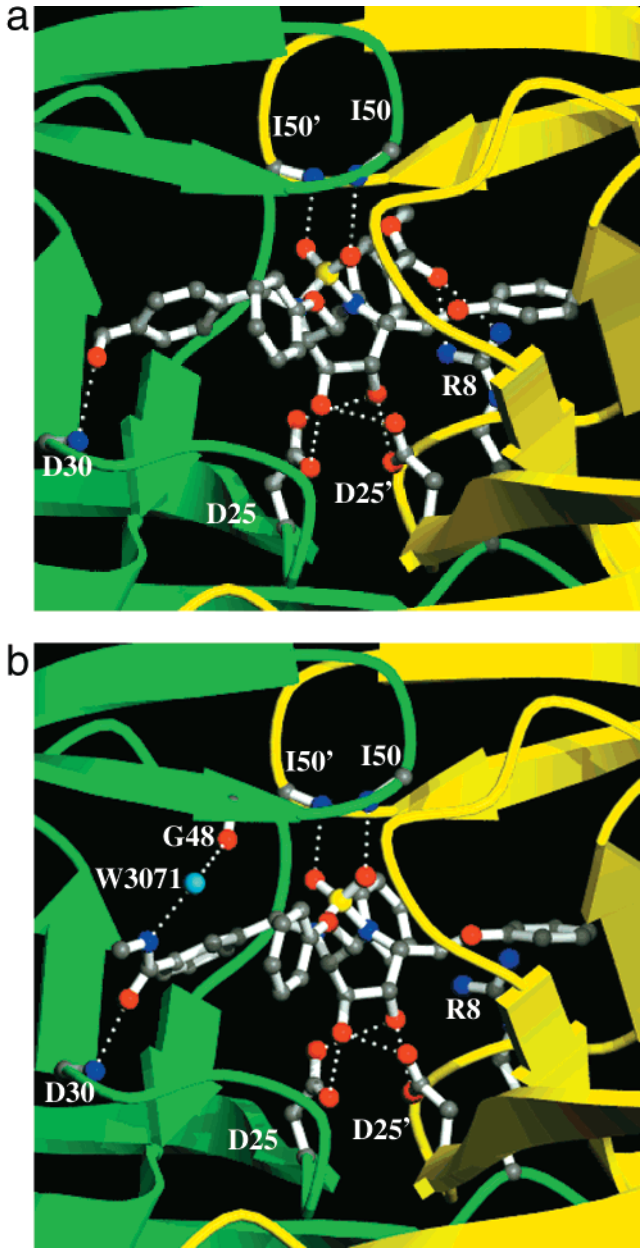


Figure 2. (a) X-ray structure of compound **21** in the HIV-1 protease active site (monomer A colored green and monomer B yellow). The inhibitor adopts a nonsymmetric conformation: i.e., the P2 side chain is located in the S2 subsite, whereas the P2′ side chain is in the S1′ subsite. Compound **21**, with a K_i of 7.3 nM, shows a flipped sulfamide conformation with the hydroxymethyl substituent interacting with the backbone amide of Asp30 (2.99 Å) in the S2 subsite and the carbonyl oxygen from the methylester with Arg8 (2.84 Å) in the S1′ subsite. The figures were drawn with the program MOLSCRIPT 2.02.[36] (b) X-ray structure of compound **16** in the HIV-1 protease active site (monomer A colored green and monomer B yellow). Similarly as for compound **21**, **16** adopts a nonsymmetric conformation: i.e., the P2 side chain is located in the S2 subsite, whereas the P2′ side chain is in the S1′ subsite. Compound **16** with a K_i of 11 nM, interacts favorably with the S2 subsite through the P2 methylamide substituent via a hydrogen bond to the backbone amide of Asp30 (2.94 Å). Moreover, the methylamide nitrogen coordinates a structural water molecule, W3071 (2.89 Å), to the backbone carbonyl of Gly48 (2.76 Å). Conserved water molecules are shown as light blue spheres. The figures were drawn with the program MOLSCRIPT 2.02.[36]

observed when the same structural alteration is performed in the DMP urea series.[33] The dimethyl substituted sulfamide inhibitor **4** (K_i = 710 nM) exhibited a 8-fold higher activity as compared to the corresponding DMP urea compound K_i = 5700 nM.[33]

An extension of the methyl P2/P2′ side chains with methylamide substituents resulted in an inactive compound (**5**). Part of the difference in K_i values for **4** and **5** could perhaps be attributed to a difference in solvation of the two compounds. Replacement of the methylamide substituents with thiazolylamide groups (**6**) gave a 10-fold improvement of the activity as compared to **5**. Since the S1/S1′ and the S2/S2′ subsites are mainly hydrophobic in character (except near to the entrance of the active site), **7** with a methylamide group in the *meta*-position of the P2/P2′ benzylic side chains was expected to yield a potent compound. Although displaying a reasonable activity (K_i = 39 nM), **7** is still slightly less potent than the parent compound **2**. Preliminary molecular modeling of inhibitor **7** in the active site of the protease provided a plausible rationale for the lower activity of **7** compared to **2**. The methylamide substituent in the *meta*-position of the P2 benzyl side chain of **7** can interact favorably with the S2 subsite through hydrogen bond formation with Asp30. For a methylamide substituent in the lipophilic S1′ subsite, no favorable hydrogen bond interactions to the protease seemed likely. Therefore, assuming a nonsymmetric conformation, it is reasonable to believe that the methylamide substituent in the S1′ subsite contributes negatively to the binding interactions between **7** and the protease. In the DMP urea series, the parent dibenzyl compound has a K_i of 3.6 nM,[34] and the introduction of methylamide substituents in the P2/P2′ side chains increases the activity 50-fold to a K_i value of 0.066 nM.[11]

The introduction of thienyl substituents provided compounds that did not meet our expectations (see Inhibitor Design). Both the *meta* thienyl substituted compound **9** (K_i = 2200 nM) and the *para* thienyl substituted compound **10** (K_i = 920 nM) exhibited low activity. The large difference in K_i value of the *meta* iodo compound **8** (K_i = 93 nM) and the *meta* thienyl compound **9** suggests that the size, shape, and electronic character of the substituent on the aryl group is of utmost importance.

Nonsymmetric Inhibitors. The first set of six nonsymmetric inhibitors, keeping benzyl as one of the P2/P2′ substituents (Table 2), clearly shows that reducing the hydrophobic interactions by substituting the benzyl group for a methyl group (**11**) leads to a sharp decrease in activity and that introduction of a amidomethyl substituent in the lipophilic environment proved to be unfavorable for the activity (**12**). Increasing the size of the amide nitrogen substituent from methyl (**12**) to thiazolyl (**13**) increased the activity.

Introduction of one thienyl-substituent in the P2′ side chain of **2**, in either the *meta* (**15**) or the *para* (**14**) position of the phenyl ring, did not result in an improved activity and in fact a slight decrease in activity as compared to **2** was observed. Furthermore, the K_i values of **15** (86 nM) and **14** (63 nM) gave no clear indication of which (*meta* or *para*) position was preferred. Introduction of one *meta*-methylamide substituent in the P2

benzyl side chain of **2** produced the most potent inhibitor (**16**) in this series with a 2-fold higher activity compared to **2**. As can be seen in the X-ray structure (Figure 2b), the methylamide substituent in this position interacts favorably with residues in the S2 subsite through hydrogen bond formations. The amide oxygen takes part in the formation of a hydrogen bond with the backbone amide of Asp30 (2.94 Å). In addition, the amide nitrogen forms a hydrogen bond interaction, coordinating a structural water molecule, W3071 (2.89 Å), to the backbone carbonyl of Gly48 (2.76 Å). Notably, inhibitor **16** is 4-fold more potent than the corresponding symmetric methylamide compound **7**. In the related urea compounds XV638 and XV655, containing a thiazolylamide instead of a methyl amide, the symmetric inhibitor (XV638) has 3 times higher activity than the nonsymmetric derivative (XV655).[13]

The final five nonsymmetric compounds (Table 2) are analogues of **2** substituted in both the P2 and P2′ positions. The inhibitory potency is largely affected by the position of the thienyl group attached to the benzyl side chain. The nonsymmetric *meta* thienyl substituted thiazolylamide compound (**18**) exhibited a K_i value of 140 nM while the *para* isomer (**19**) showed K_i of 1800 nM. These values differ considerably from the nonsymmetric *meta* (**15** $K_i = 86$ nM) and *para* (**14** $K_i = 63$ nM) thienyl benzyl compounds, where the *para* isomer has a somewhat higher activity. The combination of one *meta*- and one *para*-2-thienyl substituent (**20**) affords a compound with very poor activity (K_i 6000 nM). From preliminary modeling, assuming a nonsymmetric binding mode, we were surprised to find a very high K_i value for **20**, in fact we expected **20** to be at least of similar activity as **10**.

Alignment Based on CoMFA Study. At this point, even with access to the 3D structure of the protease, the SAR of the sulfamides is far from obvious, and to predict K_i values prior to synthesis and biological evaluation remains a challenge. To address these issues, we decided to perform a CoMFA study on the 18 inhibitors of this study along with seven related compounds from earlier studies of our laboratory[5,8] (see Tables 1−3). We assumed that all 25 compounds adopted the flipped sulfamide conformation observed in the X-ray studies.[5,8] The symmetrical inhibitors were constructed to fit the conformation of the central ring and P1/P1′ groups of **21**. The energetically preferred position of the P2/P2′ groups was determined by a Monte Carlo conformational search in the active site of the protease. Due to the previously discussed alignment problem of the 11 nonsymmetrical inhibitors, we generated CoMFA models for all 2048 (2^{11}) combinations of the 25 compounds. Overall, q^2 values varied from −0.1 to 0.7 for the 10 fields (see Methods section) used in the calculations (see Figure 3). Out of the 20 480 possible models derived from the 10 different fields used, 343 models representing 204 different alignments produced a q^2 better than 0.6. No single model rose far above the rest.

The CoMFA models were ordered by lowest error of prediction, and the top few models were inspected for their ability to rationally explain the observed activities. The first model was rejected for failing to offer an interpretable SAR. The second model, differing only in the alignment of **14**, produced a much more clear explanation of the SAR. Our hypothesis for the alignment is presented in Table 2 and Figure 4.

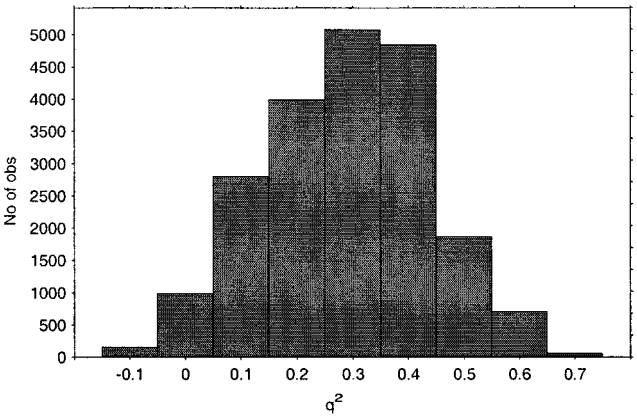


Figure 3. Distribution of q^2 values from the 20 480 CoMFA calculations used for the determination of binding mode.

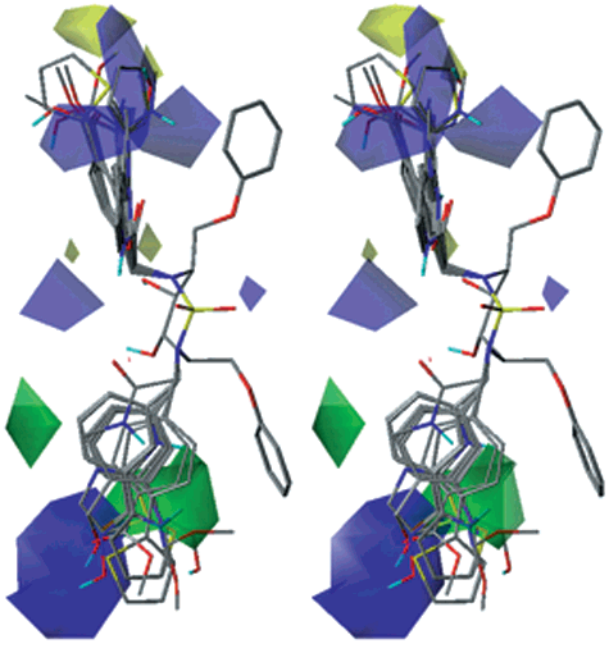


Figure 4. Chosen alignment of the 25 inhibitors based on the CoMFA calculations and contour plot (StDev*Coeff) of the steric (contoured by contribution at 80% and 20%) and electrostatic (85% and 20%) components of the parabolic CoMFA field. Regions where the model favors (green) or disfavors (yellow) steric bulk and favors (blue) or disfavors (red) positive charge are shown.

Table 4. Summary of CoMFA Validation Results

	number of components					
	1	2	3	4	5	6
	Full Model					
q^2	0.133	0.535	0.680	0.665	0.694	0.682
std err pred.	0.961	0.720	0.611	0.641	0.628	0.658
	Training Set					
q^2	−0.109	0.332	0.543	0.546	0.555	0.543
std err pred.	1.013	0.813	0.695	0.719	0.741	0.784

A summary of the CoMFA results appears in Table 4. The chosen model used the steric and electrostatic components of the parabolic field (squared magnitude of the standard CoMFA field with retained sign) with 2395 columns. Cross-validation gave a q^2 of 0.68,

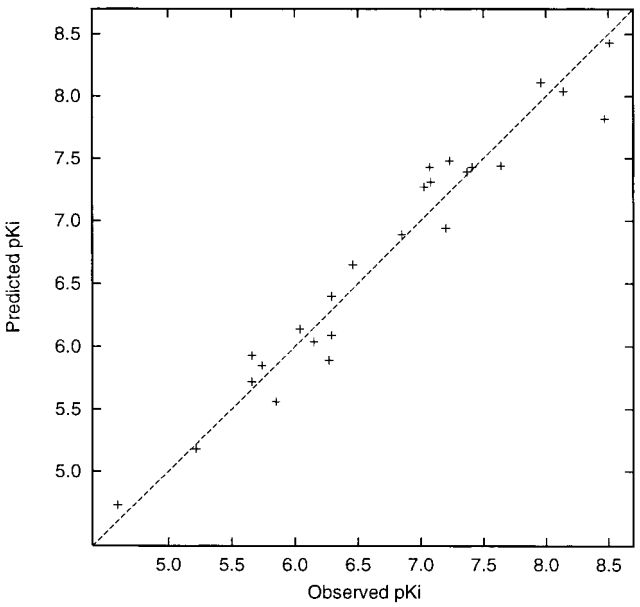


Figure 5. Plot of predicted versus actual pK_i for the 25 inhibitors of the CoMFA dataset. The mean absolute residual pK_i was 0.18.

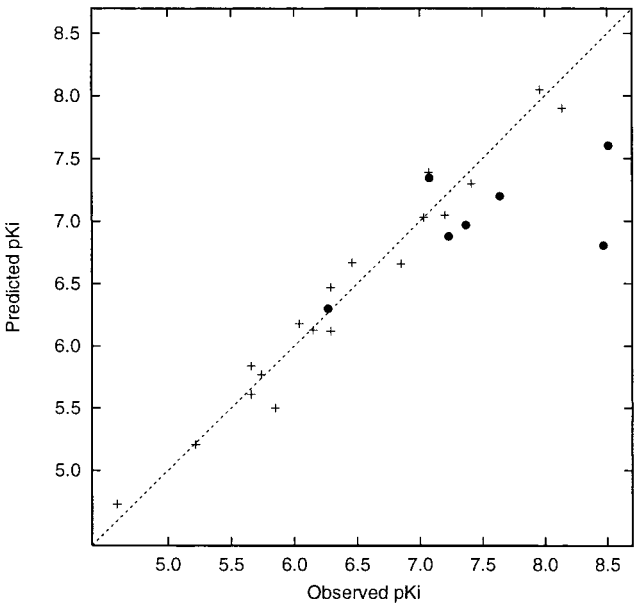


Figure 6. Plot of predicted versus actual pK_i for the 18 inhibitors of the training set used to validate the final CoMFA model. The mean absolute residual pK_i was 0.58.

standard error of prediction of 0.61, and an optimum number of components of 3. The final model on the full set of 25 inhibitors, calculated with a parabolic field (66.3% steric, 33.7% electrostatic) over 3 components, gave an r^2 of 0.95, standard error of estimate of 0.25, and F value of 121.501 (n1 = 3, n2 = 21). The mean absolute residual (pK_i) was 0.18 with a high of 0.65 for compound **3**. A plot of predicted versus actual pK_i is presented in Figure 5, and the values are given in Tables 1−3.

To validate the chosen alignment, the compounds were split into training and test sets. A CoMFA model was generated using the 18 inhibitors of the present study (Tables 1 and 2). This model used the parabolic field with 2228 columns to produce a q^2 of 0.54, standard error of prediction of 0.69, and an optimum number of components of 3. The final model of the training set, calculated with a parabolic field (66.1% steric, 33.9% electrostatic) over three components, gave an r^2 of 0.96, standard error of estimate of 0.20, and F value of 121.128 (n1 = 3, n2 = 14). The test set, comprised of the seven previously reported inhibitors (Table 3), was predicted using this model. The plot of predicted versus actual pK_i (Figure 6) shows most of the test set compounds were well predicted but compounds **3** and **25** were noticeably under predicted. These inhibitors lie outside the pK_i range of the training set. Furthermore, compound **3**, which was under predicted in the final model (Figure 5) as well, is the most chemically divergent inhibitor of the dataset. Overall, the mean absolute residual of the test set was 0.58.

Analysis of Chosen Alignment. On the basis of the alignment chosen, a good CoMFA model could be derived for our cyclic sulfamides. Further support for the alignment is reflected in the fact that both **16** and **21** adopt the same flip as seen in their respective X-ray structures in the protease (Figure 2a,b).

A contour plot (Figure 4) of the CoMFA fields of the chosen model based on all 25 inhibitors shows where the model predicts favorable (green) and unfavorable (yellow) addition of bulk. An important region for good activity appears around the S2 pocket. Figure 4 also shows where the model favors (blue) and disfavors (red) positive charge. Predictably, the most important areas for charge are located near the solvent edge. The contour plot does not highlight the importance of interaction with, e.g., Asp25/25′ or Ile50/50′ since the core of the inhibitors is unchanged throughout the series.

In the model, the benzyl groups of **11**−**16** are consistently predicted to lie in the S1′ pocket (Table 2). This is in good agreement with our initial SAR hypothesis placing more polar substituents in the S2 pocket.

Compound **20** incorporates the *meta*-thienyl of **15** and the *para*-thienyl of **14**. The dramatically lower activity of **20** can be rationalized by observing that the symmetrically substituted **9** and **10** are of comparably low activity: the thienyl group of this series does not seem to be well tolerated in the S1′ pocket. Compound **19** incorporates the nonbenzylic substituents of **13** and **14**. The thienyl group is predicted to lie in the S1′ pocket which seems to be reflected in the compound's low activity. Considering the apparent reluctance to place a thienyl in the S1′ pocket, the placement of thiazolylamidomethyl in the S2 implies that that group has even a stronger aversion for the S1′. However, compound **18**, substituting a *meta*-thienyl group for the *para*-thienyl of **19**, presents something of a surprise. Both groups would seem to prefer the S2 pocket. This apparent clash does not lower the activity but produces an activity between that of its parent compounds **13** and **15**.

Conclusion

CoMFA analysis has been used successfully to rationalize SAR data for several HIV protease inhibitor series.[35] In this study, CoMFA analysis helped us to rationalize the selection of a binding mode for the nonsymmetric compounds. The initial assumption that more polar substituents would prefer to interact with the S2 subsite agrees with our CoMFA model. But, this rule was not enough to explain why compounds **18** and

19, differing only in the position of the thienyl groups (*meta* and *para*, respectively), exhibit more than a 10-fold difference in activity. Both compounds fit the CoMFA model well even though they are predicted to adopt the opposite binding mode.

When the SAR of the cyclic urea and cyclic sulfamide inhibitors are compared, no clear relationship was found. Substituents known to produce active compounds in the urea series did not produce the desired effects in the sulfamide series. Additionally, changes that dramatically lowered the activity in the urea series produced only small effects in the sulfamide series. This clearly demonstrates that the structure−activity relationship of the two classes of inhibitors differs significantly.

Experimental Section

Chemistry. General Information. Melting points were recorded on an electrothermal melting point apparatus and are uncorrected. Optical rotations were obtained on a Perkin-Elmer 241 polarimeter. Specific rotations ($[\alpha]_D$) are reported in degrees per decimeter, and the concentration (*c*) is given in grams per 100 mL in the specific solvent. ^{1}H and ^{13}C NMR spectra were recorded on a JEOL JNM-EX 270 spectrometer at 270.2 and 67.8 MHz, respectively, or on a JEOL JNM-EX 400 spectrometer at 399.8 and 100.5 MHz, respectively. The chemical shifts are given in ppm relative to tetramethylsilane. Infrared spectra were recorded on a Perkin-Elmer 1600 series FTIR instrument. Elemental analyses were performed by MikroKemi AB, Sweden, or Analytische Laboratorien, Germany, and were within ±0.4% of calculated values. Mass spectroscopy was carried out on a JEOL SX 102 instrument. Flash column chromatography was performed on silica gel 60, 0.04−0.063 mm (E. Merck), with gradient elution unless otherwise noted. Thin-layer chromatography was performed on precoated silica gel F-254 plates (0.25 mm; E. Merck) and was visualized with UV-light and H_2SO_4 in ethanol, phosphomolybdic acid, or ninhydrin. Microwave experiments were performed in a MicroWell 10 (Personal Chemistry). Contrary to conventional conductive heating, the rise in temperature is dependent on both the volume and the geometry of the reaction mixture. The reactions were performed without stirring. ***Caution! Great care should be taken when performing pressurized microwave reactions.*** Standard workup: organic layers were dried with $MgSO_4$ and concentrated in vacuo.

(3*R*,4*S*,5*S*,6*R*)-2,7-Bismethyl-3,6-bis(phenoxymethyl)-4,5-dihydroxy-1,2,7-thiadiazepine 1,1-Dioxide (4). To a solution of compound **35** (15.0 mg, 0.032 mmol) in methanol (2 mL) was added saturated HCl in diethyl ether (0.5 mL). The reaction mixture was stirred at room temperature for 30 min. The solvent was removed, and purification by flash chromatography (CH_2Cl_2) gave compound **4** (10.7 mg, 78%). IR (KBr) ν 3512, 3454, 2897, 1600, 1497, 1466 cm^{-1}; $[\alpha]_D$ = −30.0° (*c* = 0.25, CH_3OH, 19 °C); ^{1}H NMR (270.2 MHz, acetone-d_6) δ 7.29 (dd, *J* = 8.7, 7.2 Hz, 4H), 7.00 (d, *J* = 8.7 Hz, 4H), 6.94 (t, *J* = 7.3 Hz, 2H), 4.65 (d, *J* = 4.4 Hz, 2H), 4.38−4.21 (m, 6H), 4.08 (d, *J* = 4.8 Hz, 2H), 3.06 (s, 6H); ^{13}C NMR (68.7 MHz, acetone-d_6) δ 158.2, 129.4, 121.3, 114.6, 73.2, 66.6, 53.5, 33.2. Anal. ($C_{20}H_{26}N_2O_6S$) C, H, N.

(3*R*,4*S*,5*S*,6*R*)-2,7-Bis[(*N*-methylcarbamoyl)methyl]-3,6-bis(phenoxymethyl)-4,5-dihydroxy-1,2,7-thiadiazepine 1,1-Dioxide (5). To a solution of **36** (50.0 mg, 0.088 mmol) in THF (5 mL) was added a 2 M solution of KOH in ethanol (2 mL). The reaction mixture was stirred at room temperature for 2 h. Diethyl ether and 1 M HCl (aq) were added, and the layers were separated. The water phase was extracted with diethyl ether. The combined ether extracts were washed with brine, dried, and concentrated. The crude product was used in the next step without further purification. To a solution of the crude acid (47 mg) in DMF (5 mL) were added HATU (83.6 mg, 0.220 mmol), DIEA (56.9 mg, 0.440 mmol), and a solution of methylamine in methanol (excess). The reaction mixture was stirred at room temperature overnight. Diethyl ether and water were added, the layers were separated, and the ether phase was washed with water and brine, dried, and concentrated. To a solution of the crude amide in methanol (4 mL) was added saturated HCl in diethyl ether (1 mL). The reaction mixture was stirred at room temperature for 30 min. Purification by flash chromatography (CH_2Cl_2/CH_3OH, 50:1) gave compound **5** (16.5 mg, 35%). $[\alpha]_D$ = +56.5° (*c* = 0.8, $CHCl_3$, 22 °C); ^{1}H NMR (399.2 MHz, $CDCl_3$) δ 7.26 (dd, *J* = 8.3, 7.4 Hz, 4H), 6.96 (t, *J* = 7.4 Hz, 2H), 6.90 (d, *J* = 7.8 Hz, 4H), 6.69 (brd, *J* = 4.4 Hz, 2H), 4.69 (m, 2H), 4.29 (m, 2H), 4.17 (m, 4H), 3.90 (m, 4H), 2.71 (d, *J* = 4.4 Hz, 6H); ^{13}C NMR (100.2 MHz, $CDCl_3$) δ 172.1, 157.8, 129.7, 121.7, 114.8, 73.4, 66.0, 54.8, 48.5, 26.6. Anal. ($C_{24}H_{32}N_4O_8S$) C, H, N.

***(3R,4S,5S,6R)*-3,6-Bis(phenoxymethyl)-4,5-dihydroxy-2,7-bis[(*N*-2-thiazolylcarbamoyl)methyl]-1,2,7-thiadiazepine 1,1-Dioxide (6).** To a solution of **36** (57 mg, 0.10 mmol) in THF (4 mL) was added a 2 M solution of KOH in ethanol (1.5 mL). The reaction mixture was stirred at room temperature for 2 h. Diethyl ether and 1 M HCl (aq) were added, the layers were separated, and the water phase was extracted with diethyl ether. The combined ether extracts were washed with brine, dried, and concentrated. The crude product was used in the next step without further purification. To a solution of the crude acid (54 mg) in DMF (5 mL) were added HATU (76 mg, 0.20 mmol), DIEA (65 mg, 0.50 mmol), and 2-aminothiazole (20 mg, 0.20 mmol). The reaction mixture was stirred at room temperature overnight. Diethyl ether and water were added, the layers were separated, and the ether phase was washed with water and brine, dried, and concentrated. To a solution of the crude amide in methanol (4 mL) was added saturated HCl in diethyl ether (1 mL). The reaction mixture was stirred at room temperature for 30 min. Purification by flash chromatography (CH_2Cl_2, 50:1 to CH_2Cl_2/CH_3OH, 15:1) gave compound **6** (43 mg, 64%). IR (KBr) ν 3600−3100, 2928, 1686, 1560, 1495 cm^{-1}; $[\alpha]_D$ = −13.6° (*c* = 0.48, CH_3OH, 20 °C); ^{1}H NMR (270.2 MHz, acetone-d_6) δ 11.05 (brs, 2H), 7.41 (d, *J* = 3.4 Hz, 2H), 7.23 (dd, *J* = 8.8, 7.4 Hz, 4H), 7.13 (d, *J* = 3.4 Hz, 2H), 7.08 (d, *J* = 8.8 Hz, 4H), 6.91 (t, *J* = 7.4 Hz, 2H), 5.20 (brs, 2H), 4.64 (d, *J* = 18.0 Hz, 2H), 4.61 (dd, *J* = 8.8, 6.4 Hz, 2H), 4.52 (dd, *J* = 10.2, 8.8 Hz, 2H), 4.41 (dd, *J* = 10.3, 6.4 Hz, 2H), 4.36 (d, *J* = 18.5 Hz, 2H), 4.09 (s, 2H); ^{13}C NMR (68.7 MHz, acetone-d_6) δ 169.6, 158.8, 158.4, 138.4, 130.2, 122.1, 115.8, 114.3, 73.4, 66.8, 54.4, 50.3. Anal. ($C_{28}H_{30}N_6O_8S_3$) C, H, N.

(3*R*,4*S*,5*S*,6*R*)-2,7-Bis[3-(*N*-methylcarbamoyl)benzyl]-3,6-bis(phenoxymethyl)-4,5-dihydroxy-1,2,7-thiadiazepine 1,1-Dioxide (7). Starting from **37** (92.7 mg, 0.127 mmol) compound **7** was synthesized according to the procedure outlined for compound **5**. Purification by flash chromatography (CH_2Cl_2 to CH_2Cl_2/CH_3OH, 15:1) gave compound **7** (53.0 mg, 60%); $[\alpha]_D$ = +36.6° (*c* = 0.94, CH_3OH, 22 °C); ^{1}H NMR (270.2 MHz, acetone-d_6) δ 7.94 (s, 2H), 7.69 (m, 4H), 7.55 (brs, 2H), 7.34 (apt, *J* = 7.7 Hz, 2H), 7.20 (dd, *J* = 8.6, 7.4 Hz, 4H), 6.88 (t, *J* = 7.3 Hz, 2H), 6.81 (d, *J* = 8.6 Hz, 4H), 5.06 (d, *J* = 17.1 Hz, 2H), 4.98 (brs, 2H), 4.93 (d, *J* = 17.1 Hz, 2H), 4.44 (m, 2H), 4.24 (m, 6H), 2.87 (d, *J* = 4.6 Hz, 6H); ^{13}C NMR (68.7 MHz, acetone-d_6) δ 167.8, 159.1, 141.1, 135.9, 130.7, 130.1, 129.1, 126.6, 126.3, 121.6, 115.3, 74.8, 67.0, 56.0, 52.6, 26.6. Anal. ($C_{36}H_{40}N_4O_8S$) C, H, N.

(3*R*,4*S*,5*S*,6*R*)-2,7-Bis[3-Iodobenzyl]-3,6-bis(phenoxymethyl)-4,5-dihydroxy-1,2,7-thiadiazepine 1,1-Dioxide (8). To a solution of **32** in methanol (5 mL) was added HCl in ether (10 mL), and the reaction mixture was stirred overnight and concentrated in vacuo. Purification by flash column chromatography on silica gel (CH_2Cl_2 200:1) gave a white solid (59 mg, 91%). IR (KBr) ν 3600−3200, 2926, 1599, 1496, 1301, 1240, 1148 cm^{-1}; $[\alpha]_D$ = +15.7° (*c* = 0.94, $CHCl_3$, 22 °C); ^{1}H NMR (270.2 MHz, $CDCl_3$) δ 7.69 (s, 2H), 7.53 (d, *J* = 7.9 Hz, 2H), 7.39 (d, *J* = 7.8 Hz, 2H), 7.23 (apt, 4H), 6.99 (t, *J* = 7.8 Hz, 2H) 6.95 (t, *J* = 7.4 Hz, 2H), 6.69 (d, *J* = 7.9 Hz, 4H), 4.74 (m, 4H), 4.29−4.37 (m, 6H), 4.06 (m, 2H), 3.18 (brs, 2H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 157.5, 140.7, 136.8, 136.6, 130.5,

129.8, 127.0, 121.8, 114.6, 94.6, 75.2, 67.1, 55.8, 52.6. Anal. ($C_{32}H_{32}I_2N_2O_6S$) C, H, N.

(3*R*,4*S*,5*S*,6*R*)-3,6-Bis(phenoxymethyl)-2,7-bis[3-(2-thienyl)benzyl]-4,5-dihydroxy-1,2,7-thiadiazepine 1,1-Dioxide (9). A sealed Pyrex tube was charged, under nitrogen, with **32** (50 mg, 0.06 mmol), 2-thienylboronic acid (74 mg, 0.58 mmol), $Pd(PPh_3)_4$ (6.7 mg, 0.006 mmol), 2 M Na_2CO_3 (116 μL), ethanol (90 μL), water (120 μL), and dimethoxyethane (360 μL). The reaction mixture was heated in a microwave cavity at 45 W for 3 min. After cooling, water and diethyl ether were added, and the ether extract was washed with water and brine, dried, and concentrated. The crude product was used in the next step without further purification. To the crude product in methanol (2 mL) was added saturated HCl in diethyl ether (0.5 mL). The reaction mixture was stirred at room temperature for 30 min. The solvent was removed, and purification by flash chromatography ($CHCl_3$/pentane, 2:1) gave compound **9** (29 mg, 65%). IR ($CHCl_3$) ν 3686, 3597, 3040, 2944, 1599, 1495 cm^{-1}; $[\alpha]_D = +22.3°$ ($c = 0.3$, $CHCl_3$, 22 °C); ^{1}H NMR (270.2 MHz, $CDCl_3$) δ 7.63 (s, 2H), 7.48 (d, $J = 7.2$ Hz, 2H), 7.37−7.14 (m, 12H), 7.04 (dd, $J = 4.4$, 3.6 Hz, 2H), 6.90 (t, $J = 7.2$ Hz, 2H), 6.68 (d, $J = 8.1$ Hz, 4H), 4.88 (d, $J = 16.2$ Hz, 2H), 4.79 (d, $J = 16.0$ Hz, 2H), 4.30 (m, 6H), 4.12 (m, 2H), 3.17 (d, $J = 4.8$ Hz, 2H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 157.6, 144.1, 138.8, 134.9, 129.7, 129.4, 128.2, 127.0, 125.4, 125.3, 125.1, 123.5, 121.7, 114.6, 75.4, 67.2, 56.1, 53.5. Anal. ($C_{40}H_{38}N_2O_6S_3$) C, H, N.

(3*R*,4*S*,5*S*,6*R*)-3,6-Bis(phenoxymethyl)-2,7-bis[4-(2-thienyl)benzyl]-4,5-dihydroxy-1,2,7-thiadiazepine 1,1-Dioxide (10). Starting from **33** (60 mg, 0.077 mmol), compound **10** was synthesized according to the procedure outlined for compound **9**. The solvent was removed and purification by flash chromatography (CH_2Cl_2) gave compound **10** (31.8 mg, 56%). IR (KBr) ν 3547, 3067, 2926, 1599, 1497, 1314, 1241, 1143 cm^{-1}; $[\alpha]_D = +31.1°$ ($c = 0.7$, EtOAc, 23 °C); ^{1}H NMR (270.2 MHz, acetone-d_6) δ 7.57 (m, 8H), 7.40 (m, 4H), 7.20 (dd, $J = 7.6$, 8.8 Hz, 4H), 7.08 (dd, $J = 3.8$, 4.9 Hz, 2H), 6.87 (t, $J = 7.4$ Hz, 2H), 6.83 (d, $J = 8.7$ Hz, 4H), 5.05 (d, $J = 17.3$, 2H), 4.97 (s, 2H), 4.94 (d, $J = 17.3$, 2H), 4.46 (t, $J = 6.8$ Hz, 2H), 4.26 (m, 6H); ^{13}C NMR (67.8 MHz, acetone-d_6) δ 159.1, 144.7, 140.3, 133.7, 130.1, 128.9, 128.7, 126.3, 125.5, 123.9, 121.7, 115.3, 74.7, 67.1, 55.9, 52.5. Anal. ($C_{40}H_{38}N_2O_6S_3$) C, H, N.

(3*R*,4*S*,5*S*,6*R*)-3,6-Bis(phenoxymethyl)-4,5-dihydroxy-7-methyl-2-benzyl-1,2,7-thiadiazepine 1,1-Dioxide (11). To a solution of compound **31** (30.0 mg, 0.059 mmol) and PPh_3 (38.5 mg, 0.147 mmol) in CH_2Cl_2 were added DEAD (29.7 mg, 0.147 mmol) and methanol (37.8 mg, 1.18 mmol), and the reaction mixture was stirred at room temperature for 30 min. The solvent was removed, and the crude product was filtered through silica (isohexane/CH_2Cl_2, 1:1). To the purified residue (26 mg) in methanol (2 mL) was added saturated HCl in diethyl ether (0.5 mL). The reaction mixture was stirred at room temperature for 30 min. The solvent was removed, and purification by flash chromatography (CH_2Cl_2 to CH_2Cl_2/CH_3OH, 100:1) gave compound **11** (17.7 mg, 65%). IR (KBr) ν 3511, 3031, 2946, 1599, 1499, 1440, 1363 cm^{-1}; $[\alpha]_D = -39.5°$ ($c = 1.09$, acetone, 20 °C); ^{1}H NMR (270.2 MHz, acetone-d_6) δ 7.49 (d, $J = 7.1$ Hz, 2H), 7.29 (m, 4H), 7.19 (m, 3H), 7.02 (d, $J = 8.9$ Hz, 2H), 6.95 (t, $J = 7.3$ Hz, 1H), 6.87 (t, $J = 7.3$ Hz, 1H), 6.72 (d, $J = 8.7$ Hz, 2H), 5.03 (d, $J = 17.3$ Hz, 1H), 4.89 (d, $J = 17.0$ Hz, 1H), 4.87 (d, $J = 5.0$ Hz, 1H), 4.76 (d, $J = 5.0$ Hz, 1H), 4.36 (m, 4H), 4.18 (m, 3H), 4.04 (m, 1H), 3.12 (s, 3H); ^{13}C NMR (68.7 MHz, acetone-d_6) δ 159.6, 159.3, 141.5, 130.4, 130.3, 129.2, 127.9, 127.6, 122.0, 121.8, 115.8, 115.3, 74.5, 67.5, 67.2, 55.3, 54.2, 52.8, 33.8. Anal. ($C_{26}H_{30}N_2O_6S$) C, H, N.

(3*R*,4*S*,5*S*,6*R*)-3,6-Bis(phenoxymethyl)-4,5-dihydroxy-2-[(*N*-methylcarbamoyl)methyl]-7-benzyl-1,2,7-thiadiazepine 1,1-Dioxide (12). Starting from **38** (31.0 mg, 0.052 mmol), compound **12** was synthesized according to the procedure outlined for compound **5**. Purification by flash chromatography (CH_2Cl_2/CH_3OH, 25:1) gave compound **12** (10 mg, 35%). $[\alpha]_D = +22.8°$ ($c = 0.92$, CH_3OH, 21 °C); ^{1}H NMR (270.2 MHz, acetone-d_6) δ 7.45 (m, 3H), 7.28 (m, 4H), 7.19 (m, 3H), 7.02 (d, $J = 8.9$ Hz, 2H), 6.96 (t, $J = 7.4$ Hz, 1H), 6.88 (t, $J = 7.4$ Hz, 1H), 6.74 (d, $J = 8.9$ Hz, 2H), 6.42 (d, $J = 10.5$ Hz, 1H), 5.11 (d, $J = 17.5$ Hz, 1H), 4.91 (m, 2H), 4.76 (m, 1H), 4.47 (m, 1H), 4.33 (m, 2H), 4.20 (m, 2H), 4.12 (d, $J = 17.5$ Hz, 1H), 4.02 (dd, $J = 9.5$, 5.9 Hz, 1H), 3.89 (d, $J = 17.5$ Hz, 1H), 3.85 (dd, $J = 10.5$, 3.0 Hz, 1H), 2.71 (d, $J = 5.0$ Hz, 3H); ^{13}C NMR (68.7 MHz, acetone-d_6) δ 173.1, 159.2, 159.1, 141.2, 130.3, 130.1, 129.0, 127.5, 127.4, 122.0, 121.7, 115.6, 115.2, 74.4, 73.9, 67.3, 66.7, 55.3, 54.5, 52.5, 48.2, 29.7, 26.3. Anal. ($C_{28}H_{33}N_3O_7S$) C, H, N.

(3*R*,4*S*,5*S*,6*R*)-3,6-Bis(phenoxymethyl)-4,5-dihydroxy-7-benzyl-2-[(*N*-2-thiazolylcarbamoyl)methyl]-1,2,7-thiadiazepine 1,1-Dioxide (13). Starting from **38** (21.9 mg, 0.036 mmol), compound **13** was synthesized according to the procedure outlined for compound **6**. Purification by flash chromatography (CH_2Cl_2 to CH_2Cl_2/CH_3OH, 100:1) gave compound **13** (8.5 mg, 38%). IR ($CHCl_3$) ν 3517, 3348, 3070, 1686, 1599, 1516 cm^{-1}; $[\alpha]_D = +2.1°$ ($c = 0.7$, $CHCl_3$, 21 °C); ^{1}H NMR (270.2 MHz, acetone-d_6) δ 7.45 (m, 3H), 7.30−7.10 (m, 10H), 6.94 (t, $J = 7.3$ Hz, 1H), 6.88 (t, $J = 7.4$ Hz, 1H), 6.74 (d, $J = 7.7$ Hz, 2H), 5.13 (d, $J = 17.7$ Hz, 1H), 5.08 (m, 1H), 4.96 (d, $J = 17.3$ Hz, 1H), 4.65−4.37 (m, 6H), 4.25 (m, 3H), 4.07 (m, 2H); ^{13}C NMR (68.7 MHz, acetone-d_6) δ 169.9, 159.1, 140.9, 138.5, 130.2, 130.1, 129.0, 127.5, 127.4, 122.1, 121.8, 115.8, 115.3, 114.2, 73.9, 73.8, 67.2, 66.8, 54.8, 54.5, 52.7, 50.2. Anal. ($C_{30}H_{32}N_4O_7S_2$) C, H, N.

(3*R*,4*S*,5*S*,6*R*)-3,6-Bis(phenoxymethyl)-4,5-dihydroxy-7-benzyl-2-[4-(2-thienyl)benzyl]-1,2,7-thiadiazepine 1,1-Dioxide (14). A sealed Pyrex tube was charged, under nitrogen, with **40** (28 mg, 0.04 mmol), 2-thienylboronic acid (26 mg, 0.20 mmol), $Pd(PPh_3)_4$ (4.5 mg, 0.004 mmol), 2 M Na_2CO_3 (76 μL), ethanol (59 μL), water (76 μL), and dimethoxyethane (240 μL). The reaction mixture was heated in a microwave cavity at 30 W for 4 min. After cooling, water and diethyl ether were added, and the ether extract was washed with water and brine, dried, and concentrated. The crude product was used in the next step without further purification. To the crude product in methanol (2 mL) was added saturated HCl in diethyl ether (0.5 mL). The reaction mixture was stirred at room temperature for 30 min. The solvent was removed, and purification by flash chromatography (CH_2Cl_2) gave compound **14** (16.5 mg, 63%). $[\alpha]_D = +1.42°$ ($c = 1.05$, $CHCl_3$, 22 °C); ^{1}H NMR (399.8 MHz, $CDCl_3$) δ 7.56 (d, $J = 8.3$ Hz, 2H), 7.43 (m, 4H), 7.33 (m, 2H), 7.29 (m, 3H), 7.23 (m, 4H), 7.09 (m, 1H), 6.97 (t, $J = 7.3$ Hz, 1H), 6.95 (t, $J = 7.3$ Hz, 1H), 6.72 (m, 4H), 4.86 (d, $J = 16.1$ Hz, 2H), 4.78 (d, $J = 15.6$ Hz, 2H), 4.30 (m, 6H), 4.19 (dd, $J = 8.8$, 4.4 Hz, 1H), 4.10 (dd, $J = 8.8$, 4.4 Hz, 1H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 157.6, 144.0, 137.8, 137.1, 133.9, 129.6, 128.7, 128.4, 128.1, 127.9, 127.8, 126.2, 124.9, 123.2, 121.7, 114.5, 75.4, 75.3, 66.9, 66.8, 56.2, 56.1, 53.5, 53.1. Anal. ($C_{36}H_{36}N_2O_6S_2$) C, H, N.

(3*R*,4*S*,5*S*,6*R*)-3,6-Bis(phenoxymethyl)-4,5-*O*-isopropylidene-7-benzyl-2-[3-(2-thienyl)benzyl]-1,2,7-thiadiazepine 1,1-Dioxide (15). Starting from **41** (26 mg, 0.03 mmol), compound **15** was synthesized according to the procedure outlined for compound **14**. The solvent was removed, and purification by flash chromatography (CH_2Cl_2) gave compound **15** (17 mg, 73%). $[\alpha]_D = +14.5°$ ($c = 0.73$, $CHCl_3$, 22 °C); ^{1}H NMR (399.8 MHz, $CDCl_3$) δ 7.65 (s, 1H), 7.51 (d, $J = 7.3$ Hz, 1H), 7.44 (d, $J = 7.3$ Hz, 2H), 7.39−7.18 (m, 11H), 7.07 (m, 1H), 6.97 (t, $J = 7.4$ Hz, 1H), 6.94 (t, $J = 7.4$ Hz, 1H), 6.71 (m, 4H), 4.85 (m, 4H), 4.32 (m, 6H), 4.16 (m, 1H), 4.09 (m, 1H), 3.18 (m, 2H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 157.6, 157.5, 144.0, 138.8, 137.8, 134.8, 129.6, 129.3, 128.7, 128.1, 127.9, 127.8, 126.9, 125.3, 125.2, 125.0, 123.5, 121.6, 114.5, 75.4, 75.2, 67.0, 66.9, 56.1, 56.0, 53.5, 53.2. Anal. ($C_{36}H_{36}N_2O_6S_2$) C, H, N.

(3*R*,4*S*,5*S*,6*R*)-3,6-Bis(phenoxymethyl)-4,5-dihydroxy-2-[3-(*N*-methylcarbamoyl)benzyl]-7-benzyl-1,2,7-thiadiazepine 1,1-Dioxide (16). Starting from **39** (38.8 mg, 0.057 mmol), compound **16** was synthesized according to the procedure outlined for compound **5**. Purification by flash chromatography (CH_2Cl_2/CH_3OH, 50:1 to CH_2Cl_2/CH_3OH, 15:1) gave compound **16** (17.4 mg, 48%). IR ($CHCl_3$) ν 3618, 3461, 3026,

2894, 1707, 1659, 1599, 1522, 1422 cm^{-1}; $[\alpha]_D = +7.0°$ (c = 0.88, $CHCl_3$, 19 °C); ^{1}H NMR (270.2 MHz, acetone-d_6) δ 7.94 (s, 1H), 7.71 (m, 2H), 7.60 (brs, 1H), 7.52 (d, J = 7.4 Hz, 2H), 7.39−7.17 (m, 8H), 6.90 (m, 2H), 6.81 (m, 4H), 5.11−4.91 (m, 6H), 4.45 (m, 2H), 4.31−4.13 (m, 6H), 2.89 (s, 3H); ^{13}C NMR (68.7 MHz, acetone-d_6) δ 167.8, 159.2, 159.1, 141.2, 135.9, 135.9, 130.7, 130.1, 129.1, 129.0, 127.9, 127.5, 126.6, 126.3, 121.7, 115.2, 74.7, 74.6, 67.0, 55.9, 55.7, 52.8, 52.6, 26.6. Anal. ($C_{34}H_{37}N_3O_7S$) C, H, N.

(3*R*,4*S*,5*S*,6*R*)-3,6-Bis(phenoxymethyl)-4,5-dihydroxy-7-(3-iodobenzyl)-2-[(*N*-2-thiazolylcarbamoyl)methyl]-1,2,7-thiadiazepine 1,1-Dioxide (17). To a solution of **46** (35 mg, 0.044) in methanol (2 mL) was added saturated HCl in diethyl ether (0.5 mL). The reaction mixture was stirred at room temperature for 30 min. Purification by flash chromatography (CH_2Cl_2/CH_3OH, 100:1) gave compound **17** (30.5 mg, 92%). $[\alpha]_D = +15.4°$ (c = 0.91, CH_3OH, 20 °C); ^{1}H NMR (399.8 MHz, acetone-d_6) δ 11.05 (brs, 1H), 7.90 (s, 1H), 7.50 (m, 2H), 7.44 (d, J = 3.4 Hz, 2H), 7.29 (dd, J = 8.7, 7.4 Hz, 2H), 7.22 (dd, J = 8.7, 7.4 Hz, 2H), 7.13 (m, 3H), 7.05 (apt, J = 7.8 Hz, 1H), 6.96 (t, J = 7.3 Hz, 1H), 6.90 (t, J = 7.3 Hz, 1H), 6.83 (d, J = 8.3 Hz, 2H), 5.52 (brs, 1H), 5.13 (d, J = 17.6 Hz, 1H), 5.08 (brs, 1H), 4.92 (d, J = 18.1 Hz, 1H), 4.65 (d, J = 18.1 Hz, 1H), 4.58 (m, 3H), 4.45 (m, 1H), 4.37 (d, J = 18.1 Hz, 1H), 4.27 (m, 2H), 4.18 (dd, J = 9.8, 6.8 Hz, 1H), 4.12 (d, J = 3.4 Hz, 1H); ^{13}C NMR (68.7 MHz, acetone-d_6) δ 169.9, 158.9, 158.4, 143.7, 138.5, 136.5, 136.4, 130.9, 130.2, 130.1, 127.0, 122.1, 121.7, 115.8, 115.3, 114.2, 94.6, 74.2, 73.6, 67.4, 66.8, 54.7, 54.5, 51.9, 50.2. Anal. ($C_{30}H_{31}IN_4O_7S_2$) C, H, N.

(3*R*,4*S*,5*S*,6*R*)-3,6-Bis(phenoxymethyl)-4,5-dihydroxy-2-[(*N*-2-thiazolylcarbamoyl)methyl]-7-[3-(2-thienyl)benzyl]-1,2,7-thiadiazepine 1,1-Dioxide (18). Starting from **46** (17.3 mg, 0.023 mmol), compound **18** was synthesized according to the procedure outlined for compound **14**. The solvent was removed, and purification by flash chromatography (CH_2Cl_2) gave compound **18** (8.6 mg, 53%). ^{1}H NMR (399.8 MHz, $CDCl_3$) δ 7.57 (s, 2H), 7.41 (m, 2H), 7.34−7.20 (m, 5H), 7.19−7.09 (m, 3H), 7.04−6.91 (m, 4H), 6.81 (m, 1H), 6.67 (m, 2H) 4.99 (m, 2H), 4.54 (m, 4H), 4.43−4.07 (m, 8H). Anal. ($C_{34}H_{34}N_4O_7S_3$) C, H, N.

(3*R*,4*S*,5*S*,6*R*)-3,6-Bis(benzyl)-4,5-dihydroxy-2-[(*N*-2-thiazolylcarbamoyl)methyl]-7-[4-(2-thienyl)benzyl]-1,2,7-thiadiazepine 1,1-Dioxide (19). Starting from **45** (25 mg, 0.032 mmol), compound **19** was synthesized according to the procedure outlined for compound **14**. The solvent was removed, and purification by flash chromatography (CH_2Cl_2) gave compound **19** (11 mg, 49%). IR ($CHCl_3$) ν 3686, 3341, 1686, 1599, 1545 cm^{-1}; 7.38 (m, 2H), 7.28−7.09 (m, 10H), 6.99−6.80 (m, 6H), 6.59 (m, 2H), 4.85 (m, 2H), 4.45 (m, 3H), 4.34−4.13 (m, 6H), 4.11−3.98 (m, 3H); HRMS calcd for $C_{34}H_{34}N_4O_7S_3$ (H^+) 707.1660, found 707.1668.

(3*R*,4*S*,5*S*,6*R*)-3,6-Bis(phenoxymethyl)-4,5-dihydroxy-2-[3-(2-thienyl)benzyl]-7-[4-(2-thienyl)benzyl]-1,2,7-thiadiazepine 1,1-Dioxide (20). Starting from **42** (23.8 mg, 0.031 mmol), compound **20** was synthesized according to the procedure outlined for compound **9**. The solvent was removed, and purification by flash chromatography (isohexane/CH_2Cl_2, 3:1 to CH_2Cl_2) gave compound **20** (11.0 mg, 48%). IR ($CHCl_3$) ν 3584, 3069, 2932, 1598, 1496, 1349, 1249, 1156 cm^{-1}; $[\alpha]_D = +11.6°$ (c = 0.55, $CHCl_3$, 23 °C); ^{1}H NMR (399.8 MHz, $CDCl_3$) δ 7.65 (s, 1H), 7.56 (d, J = 8.3 Hz, 2H), 7.52 (d, J = 7.8 Hz, 1H), 7.44 (d, J = 7.8 Hz, 2H), 7.36 (m, 2H), 7.28 (m, 4H), 7.22 (m, 4H), 7.10 (dd, J = 5.4, 3.9 Hz, 1H), 7.07 (dd, J = 4.9, 3.4 Hz, 1H), 6.95 (m, 2H), 6.72 (d, J = 8.5 Hz, 4H), 4.84 (m, 4H), 4.33 (m, 6H), 4.15 (m, 2H), 3.19 (brs, 2H). Anal. ($C_{40}H_{38}N_2O_6S_3$) C, H, N.

(3*R*,4*S*,5*S*,6*R*)-3,6-Bis(phenoxymethyl)-4,5-dihydroxy-7-[4-(hydroxymethyl)benzyl]-2-[4-(methoxycarbonyl)benzyl]-1,2,7-thiadiazepine-1,1-Dioxide (21). To a solution of (3*R*,4*S*,5*S*,6*R*)-2,7-bis[4-methoxycarbonyl)benzyl]-4,5-bis[(2-methoxyethoxy)methoxy]-3,6-bis(phenoxymethyl)-1,2,7-thiadiazepine 1,1-dioxide[8] (105.8 mg, 0.122 mmol) in ether (10 mL) was added $LiBH_4$ (16 mg, 0.733 mmol), and the reaction was refluxed overnight at 40 °C. The reaction was quenched with water (10 mL), and the water phase was extracted with 2 × 10 mL ether, dried, and concentrated. To the crude product in methanol (5 mL) was added HCl in ether (10 mL). The reaction mixture was stirred overnight at room temperature. Purification by flash column chromatography on silica ($CHCl_2$/CH_3OH, 100:1−25:1) gave three products: **21** (20.7 mg, 26%), **25**[8] (33.2 mg, 43%), and **26**[8] (12.8 mg, 15%). IR ($CHCl_3$) ν 3686, 3601, 3040, 2928, 1718, 1599, 1196, 1285, 1157, 1112 cm^{-1}; $[\alpha]_D = +4.2°$ (c = 0.57, $CHCl_3$, 22 °C); ^{1}H NMR (270.2 MHz, $CDCl_3$) δ 7.95 (d, J = 8.0 Hz, 2H), 7.48 (d, J = 8.3 Hz, 2H), 7.40 (d, J = 8.1 Hz, 2H), 7.24 (m, 6H), 6.96 (t, J = 7.2 Hz, 2H), 6.70 (apt, 4H), 4.84 (m, 2H), 4.78 (m, 2H), 4.60 (d, J = 5.1 Hz,), 4.12 (m, 6H), 4.07 (m, 2H), 3.87 (s, 3H), 3.15 (d, J = 5.3 Hz, 1H), 3.10 (d, J = 4.2 Hz, 1H), 1.68 (t, J = 5.7 Hz, 1H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 167.0, 157.7, 157.5, 143.5, 140.5, 137.3, 130.1, 129.7, 129.6, 129.5, 128.1, 127.5, 127.4, 121.8, 121.7, 114.6, 114.5, 75.4, 75.3, 67.0, 66.8, 65.1, 56.1, 56.0, 53.3, 52.9, 52.3. Anal. ($C_{35}H_{38}N_2O_9S$) C, H, N.

(3*R*,4*S*,5*S*,6*R*)-3,6-Bis(phenoxymethyl)-4,5-isopropylidene-1,2,7-thiadiazepine 1,1-Dioxide (28). To a solution of **27**[5] (1.68 g, 3.96 mmol) in ethyl acetate was added a catalytic amount of palladium on carbon. Hydrogen was added to the system at atmospheric pressure, and the reaction was stirred overnight. The suspension was filtered through Celite and concentrated in vacuo to give a colorless oil. The crude amine (1.45 g) in 100 mL pyridine was treated with sulfamide (380 mg, 3.95 mmol) and heated to reflux at 120 °C, using dry conditions, for 14 h. Purification by flash column chromatography on silica using CH_2Cl_2 gave the product as a white solid: 910 mg (53%). IR (KBr) ν 3311, 3064, 2985, 1599, 1496, 1241, 1165 cm^{-1}; $[\alpha]_D = +117.5°$ (c = 1.14, $CHCl_3$, 25 °C); ^{1}H NMR (270.2 MHz, $CDCl_3$) δ 7.30 (dd, J = 8.7, 7.4 Hz, 4H), 6.99 (t, J = 7.4 Hz, 2H), 6.93 (dd, J = 8.9 Hz, 4H), 5.28 (d, J = 5.4 Hz, 2H), 4.73 (dd, J = 3.8, 1.8 Hz, 2H), 4.58 (dd, J = 9.4, 6.7 Hz, 2H), 4.20 (dd, J = 9.4, 3.0 Hz, 2H), 4.11 (m, 2H), 1.34 (s, 6H); ^{13}C NMR (67.8 MHz, $CDCl_3$) 158.1, 129.7, 121.6, 114.8, 110.3, 76.4, 64.3, 52.2, 27.0. Anal. ($C_{21}H_{26}N_2O_6S$) C, H, N.

(3*R*,4*S*,5*S*,6*R*)-3,6-Bis(phenoxymethyl)-2-(4-bromobenzyl)-4,5-*O*-isopropylidene-1,2,7-thiadiazepine 1,1-Dioxide (29). To ensure high dilution conditions, 4-bromobenzylbromide (66 mg, 0.267 mmol) was dissolved in DMF (20 mL) and slowly added with a syringe pump to a solution of **28** (116 mg, 0.267 mmol) and K_2CO_3 (excess) in DMF (100 mL). The reaction mixture was stirred at room temperature overnight. Water and diethyl ether were added. The ether extract was washed with water and brine, dried, and concentrated. Purification by flash chromatography (isohexane/CH_2Cl_2, 1:1, to CH_2Cl_2) gave compound **29** (74 mg, 46%), **32** (48 mg, 23%), and unreacted starting material (11 mg, 10%). IR (KBr) ν 3392, 3039, 2934, 1591, 1496, 1462, 1384, 1237 cm^{-1}; $[\alpha]_D = +29.7°$ (c = 1.14, $CHCl_3$, 23 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (d, J = 8.3 Hz, 2H), 7.35 (apt, J = 7.8 Hz, 2H), 7.30 (d, J = 8.3 Hz, 2H), 7.27 (apt, J = 7.3 Hz, 2H), 7.04 (t, J = 7.3 Hz, 1H), 6.95 (t, J = 7.3 Hz, 1H), 6.87 (d, J = 8.8 Hz, 2H), 6.80 (d, J = 8.8 Hz, 2H), 5.14 (d, J = 3.4 Hz, 1H), 4.77 (dd, J = 9.8, 8.3 Hz, 1H), 4.71 (dd, J = 9.8, 6.8 Hz, 1H), 4.67 (d, J = 14.7 Hz, 1H), 4.46 (dd, J = 9.8, 4.4 Hz, 1H), 4.33 (dd, J = 10.2, 2.9 Hz, 1H), 4.25 (d, J = 14.2 Hz, 1H), 4.26−4.15 (m, 3H) 3.92 (m, 1H), 1.40 (s, 1H), 1.35 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.2, 157.7, 135.1, 131.9, 130.5, 129.8, 129.5, 122.2, 121.9, 120.9, 114.6, 114.4, 109.9, 75.4, 74.5, 65.1, 64.5, 58.0, 55.2, 50.3, 26.9, 26.8. Anal. ($C_{28}H_{31}BrN_2O_6S$) C, H, N.

(3*R*,4*S*,5*S*,6*R*)-3,6-Bis(phenoxymethyl)-2-(3-iodobenzyl)-4,5-*O*-isopropylidene-1,2,7-thiadiazepine 1,1-Dioxide (30). To ensure high dilution conditions, 3-iodobenzylbromide (238 mg, 0.801 mmol) was dissolved in DMF (40 mL) and slowly added with a syringe pump to a solution of **28** (350 mg, 0.806 mmol) and K_2CO_3 (excess) in DMF (150 mL). The reaction mixture was stirred at room temperature overnight. Water and diethyl ether were added. The ether extract was washed with water and brine, dried, and concentrated. Purification by flash chromatography (isohexane/CH_2Cl_2, 1:1, to CH_2Cl_2) gave compound **30** (250 mg, 48%), **33** (150 mg, 22%), and unreacted

starting material (52 mg, 15%). IR ($CHCl_3$) ν 3364, 3067, 2935, 1599, 1496 cm^{-1}; $[\alpha]_D = +48.3°$ ($c = 1.25$, $CHCl_3$, 20 °C); ^1H NMR (270.2 MHz, $CDCl_3$) δ 7.75 (s, 1H), 7.61 (d, $J = 8.3$ Hz, 1H), 7.37 (d, $J = 8.3$ Hz, 1H), 7.31 (dd, $J = 8.9$, 7.3 Hz, 2H), 7.23 (dd, $J = 8.9$, 7.3 Hz, 2H), 7.04 (apt, $J = 7.6$ Hz, 1H), 7.00 (t, $J = 7.4$ Hz, 1H), 6.91 (t, $J = 7.3$ Hz, 1H), 6.88 (d, $J = 8.9$ Hz, 2H), 6.81 (d, $J = 8.9$ Hz, 2H), 5.18 (brs, 1H), 4.69 (m, 3H), 4.48 (dd, $J = 9.9$, 4.3 Hz, 1H), 4.29 (dd, $J = 10.3$, 2.9 Hz, 1H), 4.18 (m, 4H), 3.88 (m, 1H), 1.38 (s, 3H), 1.35 (s, 3H); ^{13}C NMR (270.2 MHz, $CDCl_3$) δ 158.4, 157.8, 138.5, 137.5, 137.3, 130.5, 129.9, 129.5, 128.1, 122.0, 121.0, 114.8, 114.6, 110.0, 94.7, 75.4, 74.5, 65.3, 64.6, 58.2, 55.0, 50.4, 27.0, 26.9. Anal. ($C_{28}H_{31}IN_2O_6S$) C, H, N.

(3*R*,4*S*,5*S*,6*R*)-3,6-Bis(phenoxymethyl)-4,5-*O*-isopropylidene-2-benzyl-1,2,7-thiadiazepine 1,1-Dioxide (31). To ensure high dilution conditions, benzylbromide (39.0 mg, 0.230 mmol) was dissolved in DMF (10 mL) and slowly added with a syringe pump to a solution of **28** (100 mg, 0.230 mmol) and K_2CO_3 (excess) in DMF (30 mL). The reaction mixture was stirred at room temperature overnight. Water and diethyl ether were added. The ether extract was washed with water and brine, dried, and concentrated. Purification by flash chromatography (isohexane/CH_2Cl_2, 1:1, to CH_2Cl_2) gave compound **31** (70.1 mg, 58%), **34** (25.1 mg, 18%), and unreacted starting material (20.1 mg, 20%). IR ($CHCl_3$) ν 3365, 3017, 2935, 1599, 1496, 1457, 1382 cm^{-1}; $[\alpha]_D = +42.2°$ ($c = 1.02$, $CHCl_3$, 22 °C); ^1H NMR (270.2 MHz, $CDCl_3$) δ 7.44−7.19 (m, 9H), 7.00 (t, $J = 7.2$ Hz, 1H), 6.91 (t, $J = 7.4$ Hz, 1H), 6.84 (d, $J = 8.7$ Hz, 2H), 6.80 (d, $J = 8.7$ Hz, 2H), 5.11 (d, $J = 3.1$ Hz, 1H), 4.69 (m, 3H), 4.36 (m, 3H), 4.16 (m, 3H), 3.97 (m, 1H), 1.36 (s, 3H), 1.30 (s, 3H); ^{13}C NMR (68.7 MHz, $CDCl_3$) δ 158.5, 157.8, 136.1, 129.8, 129.5, 128.9, 128.3, 121.9, 120.9, 114.8, 114.5, 109.8, 75.6, 74.5, 65.3, 65.0, 57.9, 56.0, 50.4, 26.9. Anal. ($C_{28}H_{32}N_2O_6S$) C, H, N. **(3*R*,4*S*,5*S*,6*R*)-2,7-Dibenzyl-3,6-bis(phenoxymethyl)-4,5-*O*-isopropylidene-1,2,7-thiadiazepine 1,1-Dioxide (34).** ^1H NMR (270.2 MHz, $CDCl_3$) δ 7.46−7.21 (m, 14H), 6.94 (t, $J = 7.4$ Hz, 2H), 6.83 (d, $J = 7.8$ Hz, 4H), 4.94 (m, 2H), 4.73 (d, $J = 15.8$ Hz, 2H), 4.61 (d, $J = 15.2$ Hz, 2H), 4.53 (dd, $J = 10.5$, 4.3 Hz, 2H), 4.21 (dd, $J = 10.4$, 3.7 Hz, 2H), 3.87 (m, 2H) 1.28 (s, 6H); ^{13}C NMR (68.7 MHz, $CDCl_3$) δ 158.2, 136.1, 129.5, 128.7, 128.2, 127.9, 121.1, 114.4, 109.7, 74.7, 64.0, 55.3, 53.9, 26.9. Anal. ($C_{35}H_{38}N_2O_6S$) C, H, N.

(3*R*,4*S*,5*S*,6*R*)-2,7-Bis(4-bromobenzyl)-3,6-bis(phenoxymethyl)-4,5-*O*-isopropylidene-1,2,7-thiadiazepine 1,1-Dioxide (32). To a solution of **28** (80 mg, 0.18 mmol) in DMF (5 mL) were added 4-bromobenzylbromide (184 mg, 0.74 mmol) and K_2CO_3 (excess). The reaction mixture was stirred overnight. Water and diethyl ether were added, and the ether extract was washed with water and brine, dried, and concentrated. Purification by flash chromatography (isohexane/CH_2Cl_2, 1:1, to isohexane/CH_2Cl_2, 1:3) gave compound **32** (118 mg, 85%). IR (KBr) ν 3064, 2936, 1597, 1495, 1349, 1241, 1145 cm^{-1}; $[\alpha]_D = +25.9°$ ($c = 1.16$, $CHCl_3$, 23 °C); ^1H NMR (399.8 MHz, $CDCl_3$) δ 7.47 (d, $J = 8.3$ Hz, 4H), 7.30 (m, 8H), 6.99 (t, $J = 7.3$ Hz, 2H), 6.84 (d, $J = 8.3$ Hz, 4H), 4.90 (m, 2H), 4.60 (m, 6H) 4.23 (dd, $J = 10.7$, 3.6 Hz, 2H), 3.88 (m, 2H), 1.33 (s, 6H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 158.0, 135.3, 131.9, 130.0, 129.7, 122.1, 121.3, 114.4, 110.0, 74.8, 63.9, 55.7, 53.5, 27.0. Anal. ($C_{35}H_{36}Br_2N_2O_6S$) C, H, N.

(3*R*,4*S*,5*S*,6*R*)-2,7-Bis(3-iodobenzyl)-3,6-bis(phenoxymethyl)-4,5-isopropylidene-1,2,7-thiadiazepine 1,1-Dioxide (33). To a solution of **28** (66 mg, 0.152 mmol) in DMF (4 mL) was added sodium hydride (18 mg, 0.608 mmol). The reaction mixture was stirred under nitrogen atmosphere for 10 min. To the reaction mixture was added 3-iodobenzylbromide (180.6 mg, 0.608 mmol), and the reaction was stirred overnight. The reaction mixture was diluted with water (15 mL) and extracted with ether, and the combined ether extracts were dried and concentrated. Purification by flash column chromatography (isohexane/CH_2Cl_2 1:1) gave compound **32** as a colorless oil (86.6 mg, 67%). IR (KBr) ν 3023, 2931, 1598, 1496, 1353, 1240 cm^{-1}; $[\alpha]_D = +33.7°$ ($c = 1.5$, $CHCl_3$, 22°C); ^1H NMR (270.2 MHz, $CDCl_3$) δ 7.73 (s, 2H), 7.61 (d, $J = 8.4$ Hz, 2H), 7.39 (d, $J = 8.2$ Hz, 2H), 7.27 (dd, $J = 8.6$, 7.4 Hz, 4H), 7.05 (apt, $J = 7.7$ Hz, 2H), 6.95 (apt, $J = 7.4$ Hz, 2H), 6.84 (d, $J = 8.6$ Hz, 4H), 4.90 (m, 2H), 4.56 (aps, 4H), 4.55 (dd, $J = 10.4$, 4.9 Hz, 2H), 4.19 (dd, $J = 10.4$, 3.6 Hz), 3.87 (m, 2H), 1.31 (s, 6H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 158.1, 138.8, 137.2, 137.1, 130.6, 129.7, 127.6, 121.4, 114.6, 110.1, 94.7, 74.9, 64.0, 56.1, 53.4, 27.1. Anal. ($C_{35}H_{36}I_2N_2O_6S$) C, H, N.

(3*R*,4*S*,5*S*,6*R*)-2,7-Bis(methyl)-3,6-bis(phenoxymethyl)-4,5-*O*-isopropylidene-1,2,7-thiadiazepine 1,1-Dioxide (35). To a solution of **28** (20.0 mg, 0.046 mmol) and PPh_3 (60.3 mg, 0.230 mmol) in CH_2Cl_2 were added DEAD (42.0 mg, 0.230 mmol) and methanol (29.4 mg, 0.920 mmol), and the reaction mixture was stirred at room temperature for 30 min. The solvent was removed, and purification by flash chromatography (isohexane/CH_2Cl_2, 3:1, to CH_2Cl_2) gave compound **35** (17.8 mg, 84%). IR ($CHCl_3$) ν 3044, 2937, 1598, 1496, 1468, 1375, 1258 cm^{-1}; $[\alpha]_D = +100.5°$ ($c = 0.99$, $CHCl_3$, 22°C); ^1H NMR (270.2 MHz, $CDCl_3$) δ 7.28 (dd, $J = 8.5$, 7.4 Hz, 4H), 6.95 (t, $J = 7.2$ Hz, 2H), 6.92 (d, $J = 8.6$ Hz, 4H), 4.72 (m, 2H), 4.53 (dd, $J = 10.6$, 6.2 Hz, 2H), 4.31 (dd, $J = 10.5$, 3.5 Hz, 2H), 3.95 (m, 2H), 3.09 (s, 6H), 1.34 (s, 6H); ^{13}C NMR (68.7 MHz, $CDCl_3$) δ 158.3, 129.7, 121.4, 114.8, 109.8, 75.5, 64.8, 58.5, 38.1, 27.0. Anal. ($C_{23}H_{30}N_2O_6S$) C, H, N.

(3*R*,4*S*,5*S*,6*R*)-2,7-Bis(methoxycarbonylmethyl)-3,6-bis(phenoxymethyl)-4,5-*O*-isopropylidene-1,2,7-thiadiazepine 1,1-Dioxide (36). To a solution of **28** (70.0 mg, 0.16 mmol) in DMF (5 mL) were added methylbromoacetate (98.7 mg, 0.645 mmol) and K_2CO_3 (excess). The reaction mixture was stirred at room temperature overnight. Diethyl ether and water were added, the layers were separated, and the ether phase was washed with water and brine, dried, and concentrated. Purification by flash chromatography (CH_2Cl_2) gave compound **36** (74.4 mg, 82%). IR (KBr) ν 3038, 2952, 1751, 1599, 1497, 1376, 1240, 1156 cm^{-1}; $[\alpha]_D = +48.8°$ ($c = 1.06$, $CHCl_3$, 23 °C); ^1H NMR (270.2 MHz, $CDCl_3$) δ 7.27 (dd, $J = 8.5$, 7.6 Hz, 4H), 6.95 (t, $J = 7.5$ Hz, 2H), 6.89 (d, $J = 8.1$ Hz, 4H), 4.82 (m, 2H), 4.58 (dd, $J = 10.3$, 7.0 Hz, 2H), 4.39 (d, $J = 18.6$, 2H), 4.31 (dd, $J = 10.0$, 2.6 Hz, 2H), 4.21 (d, $J = 18.6$, 2H), 4.19 (m, 2H), 3.67 (s, 6H), 1.33 (s, 6H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 170.6, 158.1, 129.7, 121.4, 114.6, 110.2, 76.3, 65.2, 57.6, 52.4, 51.4, 27.1. Anal. ($C_{27}H_{34}N_2O_{10}S$) C, H, N.

(3*R*,4*S*,5*S*,6*R*)-3,6-Bis(phenoxymethyl)-4,5-*O*-isopropylidene-2,7-[3-(methoxycarbonyl)benzyl]-1,2,7-thiadiazepine 1,1-Dioxide (37). To a solution of **28** (69 mg, 0.16 mmol) in DMF (10 mL) were added methyl-3-bromomethylbenzoate (146 mg, 0.64 mmol) and K_2CO_3 (excess). The reaction mixture was stirred at room temperature overnight. Water and diethyl ether were added. The ether extract was washed with water and brine, dried, and concentrated. Purification by flash chromatography (isohexane/CH_2Cl_2, 3:1, to CH_2Cl_2) gave compound **37** (91.4 mg, 79%). IR (KBr) ν 3035, 2986, 1722, 1599, 1497, 1449, 1354, 1290, 1241 cm^{-1}; $[\alpha]_D = +52.3$ ° ($c = 1.28$, $CHCl_3$, 23 °C); ^{1}HNMR (270.2 MHz, $CDCl_3$) δ 8.03 (s, 2H), 7.95 (d, $J = 7.8$ Hz, 2H), 7.70 (d, $J = 8.1$ Hz, 2H), 7.43 (t, $J = 7.7$ Hz, 2H), 7.24 (dd, $J = 8.6$, 7.4 Hz, 4H), 6.94 (t, $J = 7.4$ Hz, 2H), 6.80 (d, $J = 8.9$ Hz, 4H), 4.93 (m, 2H), 4.70 (brs, 4H), 4.56 (dd, $J = 10.5$, 5.1 Hz, 2H), 4.19 (dd, $J = 10.4$, 3.6 Hz, 2H), 3.88 (s, 6H), 1.29 (s, 6H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 166.9, 158.2, 136.9, 133.0, 130.7, 129.7, 129.4, 129.3, 129.1, 121.3, 114.6, 110.1, 74.9, 64.0, 56.1, 53.9, 52.3, 27.1. Anal. ($C_{39}H_{42}N_2O_{10}S$) C, H, N.

(3*R*,4*S*,5*S*,6*R*)-3,6-Bis(phenoxymethyl)-4,5-*O*-isopropylidene-2-methoxycarbonylmethyl-7-benzyl-1,2,7-thiadiazepine 1,1-Dioxide (38). To a solution of **31** (51.6 mg, 0.098 mmol) in DMF (5 mL) were added methylbromoacetate (60.0 mg, 0.392 mmol) and K_2CO_3 (excess). The reaction mixture was stirred at room temperature overnight. Diethyl ether and water were added, the layers were separated, and the ether phase was washed with water and brine, dried, and concentrated. Purification by flash chromatography (CH_2Cl_2) gave compound **38** (53.3 mg, 91%). IR ($CHCl_3$) ν 3058, 2954, 1751, 1599, 1497, 1456, 1353 cm^{-1}; $[\alpha]_D = +58.7°$ ($c = 0.98$, $CHCl_3$, 20 °C); ^1H NMR (270.2 MHz, $CDCl_3$) δ 7.41−7.25 (m, 7H), 7.19 (dd, $J = 8.0$, 7.6 Hz, 2H), 6.98 (t, $J = 7.3$ Hz, 1H),

6.89 (m, 3H), 6.73 (d, J = 8.3 Hz, 2H), 5.03 (dd, J = 9.9, 5.8 Hz, 1H), 4.82 (d, J = 15.5 Hz, 1H), 4.72 (dd, J = 9.9, 5.8 Hz, 1H), 4.54 (dd, J = 10.4, 6.2 Hz, 1H), 4.50 (dd, J = 10.3, 5.8 Hz, 1H), 4.36−4.23 (m, 5H), 4.15 (m, 1H), 3.99 (m, 1H), 3.63 (s, 3H), 1.34 (s, 6H); ^{13}C NMR (68.7 MHz, $CDCl_3$) δ 170.6, 158.4, 150.8, 136.5, 129.9, 129.5, 128.8, 128.5, 128.1, 121.7, 121.0, 114.7, 114.6, 110.2, 75.6, 74.8, 65.4, 65.2, 57.5, 56.7, 54.5, 53.7, 52.4, 51.6, 27.2, 27.1. Anal. ($C_{31}H_{36}N_2O_8S$) C, H, N.

(3*R*,4*S*,5*S*,6*R*)-3,6-Bis(phenoxymethyl)-4,5-*O*-isopropylidene-2-[3-(methoxycarbonyl)benzyl]-7-benzyl-1,2,7-thiadiazepine 1,1-Dioxide (39). To a solution of **31** (50 mg, 0.095 mmol) in DMF (10 mL) were added methyl-3-bromomethylbenzoate (43.6 mg, 0.191 mmol) and K_2CO_3 (excess). The reaction mixture was stirred at room temperature overnight. Water and diethyl ether were added. The ether extract was washed with water and brine, dried, and concentrated. Purification by flash chromatography (isohexane/CH_2Cl_2, 3:1, to isohexane/CH_2Cl_2, 1:2) gave compound **39** (47.4 mg, 74%). IR ($CHCl_3$) ν 3061, 2953, 1720, 1599, 1497, 1436, 1354, 1291 cm^{-1}; $[\alpha]_D$ = +48.5° (c = 1.15, $CHCl_3$, 20 °C); ^{1}H NMR (270.2 MHz, $CDCl_3$) δ 8.03 (s, 1H), 7.96 (d, J = 7.8 Hz, 1H), 7.71 (d, J = 7.8 Hz, 1H), 7.46−7.19 (m, 10H), 6.96 (t, J = 7.6 Hz, 1H), 6.92 (t, J = 7.6 Hz), 6.84 (d, J = 8.6 Hz, 2H), 6.79 (d, J = 8.6 Hz, 2H), 4.93 (m, 2H), 4.83−4.61 (m, 3H), 4.55 (m, 3H), 4.23 (dd, J = 3.8, 1.7 Hz, 1H), 4.18 (dd, J = 3.6, 1.6 Hz, 1H), 1.30 (s, 6H); ^{13}C NMR (68.7 MHz, $CDCl_3$) δ 167.0, 158.3, 137.0, 136.3, 133.1, 130.7, 129.8, 129.7, 129.4, 129.1, 129.0, 128.4, 128.2, 121.4, 121.3, 114.7, 110.0, 74.9, 64.2, 64.1, 56.2, 55.5, 54.2, 53.9, 52.4, 27.1. Anal. ($C_{37}H_{40}N_2O_8S$) C, H, N.

(3*R*,4*S*,5*S*,6*R*)-3,6-Bis(phenoxymethyl)-2-(4-bromobenzyl)-4,5-*O*-isopropylidene-7-benzyl-1,2,7-thiadiazepine 1,1-Dioxide (40). To a solution of **29** (50 mg, 0.08 mmol) in DMF (3 mL) were added benzylbromide (56 mg, 0.33 mmol) and K_2CO_3 (excess). The reaction mixture was stirred overnight. Water and diethyl ether were added, and the ether extract was washed with water and brine, dried, and concentrated. Purification by flash chromatography (isohexane/CH_2Cl_2, 1:1, to isohexane/CH_2Cl_2, 1:3) gave compound **40** (43 mg, 75%). $[\alpha]_D$ = +28.0° (c = 0.75, CHCl3, 22 °C); ^{1}H NMR (270.2 MHz, $CDCl_3$) δ 7.43 (m, 4H), 7.38−7.23 (m, 9H), 6.95 (t, J = 7.3 Hz, 2H), 6.82 (m, 4H), 4.92 (m, 2H), 4.75 (d, J = 15.8 Hz, 1H), 4.56 (m, 5H), 4.22 (t, J = 3.6 Hz, 1H), 4.18 (t, J = 3.6 Hz, 1H), 3.87 (m, 2H), 1.30 (s, 3H), 1.29 (s, 3H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 158.3, 158.2, 136.2, 135.5, 131.9, 130.1, 129.7, 128.9, 128.4, 128.1, 122.1, 121.3, 114.6, 114.5, 110.0, 74.9, 74.8, 64.2, 64.0, 55.9, 55.5, 54.1, 53.6, 27.0. Anal. ($C_{35}H_{37}BrN_2O_6S$) C, H, N.

(3*R*,4*S*,5*S*,6*R*)-3,6-Bis(phenoxymethyl)-2-(3-iodobenzyl)-4,5-*O*-isopropylidene-7-benzyl-1,2,7-thiadiazepine 1,1-Dioxide (41). To a solution of **30** (62 mg, 0.09 mmol) in DMF (3 mL) were added benzylbromide (65 mg, 0.38 mmol) and K_2CO_3 (excess). The reaction mixture was stirred overnight. Water and diethyl ether were added, and the ether extract was washed with water and brine, dried, and concentrated. Purification by flash chromatography (isohexane/CH_2Cl_2, 1:1, to isohexane/CH_2Cl_2, 1:3) gave compound **41** (68 mg, 97%). $[\alpha]_D$ = +39.6° (c = 1.07, $CHCl_3$, 20 °C); ^{1}H NMR (399.8 MHz, $CDCl_3$) δ 7.78 (m, 1H), 7.64 (d, J = 7.8 Hz, 1H), 7.45 (m, 3H), 7.39−7.28 (m, 7H), 7.09 (m, 1H), 6.99 (t, J = 7.3 Hz, 1H), 6.98 (t, J = 7.3 Hz, 1H), 6.88 (m, 4H), 4.96 (m, 2H), 4.79 (d, J = 15.6 Hz, 1H), 4.59 (m, 5H), 4.24 (m, 2H), 3.91 (m, 2H), 1.34 (s, 3H), 1.32 (s, 3H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 158.2, 158.1, 138.9, 137.1, 136.1, 130.5, 129.6, 128.8, 128.3, 128.1, 127.5, 121.3, 114.6, 114.5, 109.9, 94.6, 74.8, 64.1, 63.9, 56.1, 55.4, 54.1, 53.3, 27.0, 26.9. Anal. ($C_{35}H_{37}IN_2O_6S$) C, H, N.

(3*R*,4*S*,5*S*,6*R*)-3,6-Bis(phenoxymethyl)-2-(3-bromobenzyl)-7-(4-bromobenzyl)-4,5-*O*-isopropylidene-1,2,7-thiadiazepine 1,1-Dioxide (42). To a solution of **29** (32.2 mg, 0.053 mmol) in DMF (3 mL) were added 3-bromobenzylbromide (40.0 mg, 0.160 mmol) and K_2CO_3 (excess). The reaction mixture was stirred overnight. Water and diethyl ether were added, and the ether extract was washed with water and brine, dried, and concentrated. Purification by flash chromatography (isohexane/CH_2Cl_2, 2:1, to isohexane/CH_2Cl_2, 1:3) gave compound **42** (34.8 mg, 85%). IR (KBr) ν 3063, 2932, 1597, 1495, 1353, 1241, 1155 cm^{-1}; $[\alpha]_D$ = +29.4° (c = 1.28, $CHCl_3$, 22 °C); ^{1}H NMR (270.2 MHz, $CDCl_3$) δ 7.56 (s, 1H), 7.47−7.33 (m, 4H), 7.31−7.16 (m, 7H), 6.96 (m, 2H), 6.82 (m, 4H), 4.89 (m, 2H), 4.56 (m, 6H), 4.18 (m, 2H), 3.87 (m, 2H), 1.30 (s, 6H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 158.1, 138.7, 135.3, 132.0, 131.3, 130.4, 130.1, 129.7, 126.9, 122.9, 122.1, 121.4, 114.6, 114.5, 110.0, 74.9, 63.9, 63.8, 56.1, 55.8, 53.5, 27.0. Anal. ($C_{35}H_{36}Br_2N_2O_6S$) C, H, N.

(3*R*,4*S*,5*S*,6*R*)-3,6-Bis(phenoxymethyl)-2-(4-bromobenzyl)-4,5-*O*-isopropylidene-7-methoxycarbonylmethyl-1,2,7-thiadiazepine 1,1-Dioxide (43). To a solution of **29** (73.6 mg, 0.122 mmol) in DMF (5 mL) were added methylbromoacetate (56.0 mg, 0.366 mmol) and K_2CO_3 (excess). The reaction mixture was stirred at room temperature overnight. Diethyl ether and water were added, the layers were separated, and the ether phase was washed with water and brine, dried, and concentrated. Purification by flash chromatography (isohexane/CH_2Cl_2, 1:3) gave compound **43** (74.3 mg, 90%). IR (KBr) ν 3038, 2986, 1753, 1598, 1496, 1376, 1243 cm^{-1}; $[\alpha]_D$ = +47.3° (c = 1.14, $CHCl_3$, 23 °C); ^{1}H NMR (270.2 MHz, acetone-d_6) δ 7.40 (d, J = 8.3 Hz, 2H), 7.24 (m, 6H), 6.95 (m, 4H), 6.71 (d, J = 8.3 Hz, 2H), 5.00 (dd, J = 9.7, 5.6 Hz, 1H), 4.78 (d, J = 15.7 Hz, 1H), 4.70 (dd, J = 9.9, 5.9 Hz, 1H), 4.56 (dd, J = 10.8, 6.8 Hz, 1H), 4.51 (dd, J = 10.2, 5.7 Hz, 1H), 4.32 (brs, 2H), 4.25 (m, 2H), 4.23 (d, J = 15.9 Hz, 1H), 4.13 (m, 1H), 3.97 (m, 1H), 3.61 (s, 3H), 1.36 (s, 3H), 1.34 (s, 3H); ^{13}C NMR (67.8 MHz, acetone-d_6) δ 170.5, 158.1, 157.9, 135.7, 131.7, 130.1, 129.8, 129.5, 121.9, 121.7, 121.0, 114.6, 114.5, 110.2, 75.6, 74.8, 65.2, 64.7, 57.6, 56.8, 53.7, 52.4, 51.6, 27.1, 27.0. Anal. ($C_{31}H_{35}BrN_2O_8S$) C, H, N.

(3*R*,4*S*,5*S*,6*R*)-3,6-Bis(phenoxymethyl)-7-(3-iodobenzyl)-4,5-*O*-isopropylidene-2-methoxycarbonylmethyl-1,2,7-thiadiazepine 1,1-Dioxide (44). To a solution of **30** (200 mg, 0.31 mmol) in DMF (10 mL) were added methylbromoacetate (236 mg, 1.53 mmol) and K_2CO_3 (excess). The reaction mixture was stirred at room temperature overnight. Diethyl ether and water were added, the layers were separated, and the ether phase was washed with water and brine, dried, and concentrated. Purification by flash chromatography (isohexane/CH_2Cl_2, 3:1) gave compound **44** (190 mg, 85%). IR ($CHCl_3$) ν 3043, 2954, 1751, 1599, 1497 cm^{-1}; $[\alpha]_D$ = +41.5° (c = 1.1, $CHCl_3$, 20 °C); ^{1}H NMR (270.2 MHz, $CDCl_3$) δ 7.71 (s, 1H), 7.58 (d, J = 7.9 Hz, 1H), 7.35 (d, J = 7.9 Hz, 1H), 7.30 (dd, J = 8.6, 7.2 Hz, 2H), 7.21 (dd, J = 8.6, 7.6 Hz, 2H), 7.01 (apt, J = 7.4 Hz, 1H), 6.98 (t, J = 7.6 Hz, 1H), 6.90 (t, J = 7.6 Hz, 1H), 6.88 (d, J = 8.9 Hz, 2H), 6.75 (d, J = 8.9 Hz, 2H), 4.99 (dd, J = 9.9, 5.6 Hz, 1H), 4.79 (d, J = 15.8 Hz, 1H), 4.71 (dd, J = 9.9, 5.9 Hz, 1H), 4.56 (dd, J = 10.5, 6.9 Hz, 1H), 4.51 (dd, J = 10.2, 5.9 Hz, 1H), 4.35−4.19 (m, 5H), 4.13 (m, 1H), 3.99 (m, 1H), 3.61 (s, 3H), 1.36 (s, 3H), 1.34 (s, 3H); ^{13}C NMR (68.7 MHz, $CDCl_3$) δ 170.5, 158.1, 157.9, 139.0, 137.1, 137.0, 130.3, 129.8, 129.5, 127.6, 121.7, 121.0, 114.7, 114.5, 110.2, 94.5, 75.5, 74.8, 65.3, 64.6, 57.6, 57.0, 53.5, 52.4, 51.6, 27.1, 27.0. Anal. ($C_{31}H_{35}IN_2O_8S$) C, H, N.

(3*R*,4*S*,5*S*,6*R*)-3,6-Bis(phenoxymethyl)-7-(4-bromobenzyl)-4,5-*O*-isopropylidene-2-[(*N*-2-thiazolylcarbamoyl)-methyl]-1,2,7-thiadiazepine 1,1-Dioxide (45). To a solution of **43** (36.0 mg, 0.053 mmol) in THF (5 mL) was added a 2 M solution of KOH in ethanol (3 mL). The reaction mixture was stirred at room temperature for 2 h. Diethyl ether and 1 M HCl (aq) were added, the layers were separated, and the water phase was extracted with diethyl ether. The combined ether extracts were washed with brine, dried, and concentrated. The crude product was used in the next step without further purification. To a solution of the crude acid (35 mg) in DMF (5 mL) were added PyBop (42.6 mg, 0.082 mmol), TEA (13.7 mg, 0.135 mmol), and 2-aminothiazole (8.2 mg, 0.082). The reaction mixture was stirred at room temperature overnight. Diethyl ether and water were added, the layers were separated, and the ether phase was washed with water and brine, dried, and concentrated. Purification by flash chromatography (CH_2Cl_2 to CH_2Cl_2/CH_3OH, 100:1) gave compound **45** (19.0 mg, 47%). IR (KBr) ν 3320, 3039, 2933, 1700, 1599, 1541, 1496,

1380, 1239, 1156 cm^{-1}; $[\alpha]_D = +17.6°$ ($c = 1.15$, $CHCl_3$, 23 °C); ^1H NMR (270.2 MHz, $CDCl_3$) δ 7.48 (d, $J = 3.6$ Hz, 1H), 7.43 (d, $J = 8.4$ Hz, 2H), 7.29 (m, 4H), 7.21 (d, $J = 8.2$ Hz, 2H), 7.13 (d, $J = 8.7$ Hz, 2H), 6.98 (m, 3H), 6.86 (d, $J = 8.9$ Hz, 2H), 4.93−4.63 (m, 4H), 4.55 (dd, $J = 10.7$, 3.8 Hz, 1H), 4.49 (d, $J = 18.3$ Hz, 1H), 4.44 (d, $J = 16.0$ Hz, 1H), 4.36 (dd, $J = 10.4$, 4.1 Hz, 1H), 4.13 (m, 2H), 4.04 (d, $J = 18.0$ Hz, 1H), 3.82 (m, 1H), 1.39 (s, 3H), 1.30 (s, 3H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 166.6, 157.9, 157.8, 137.5, 135.0, 132.1, 130.0, 129.9, 129.6, 122.2, 121.9, 121.7, 115.0, 114.5, 114.1, 110.2, 75.1, 74.7, 64.2, 63.1, 59.2, 55.4, 53.6, 53.4, 27.1, 26.9. Anal. ($C_{33}H_{35}BrN_4O_7S_2$) C, H, N.

(3*R*,4*S*,5*S*,6*R*)-3,6-Bis(phenoxymethyl)-4,5-*O*-isopropylidene-7-(3-iodobenzyl)-2-[(*N*-2-thiazolylcarbamoyl)-methyl]-1,2,7-thiadiazepine 1,1-Dioxide (46). Starting from **44** (94.6 mg, 0.131 mmol), compound **46** was synthesized according to the procedure outlined for compound **45**. Purification by flash chromatography (CH_2Cl_2/CH_3OH, 200:1) gave compound **46** (72 mg, 69%). $[\alpha]_D = +19.3°$ ($c = 1.05$, $CHCl_3$, 21 °C); ^1H NMR (270.2 MHz, $CDCl_3$) δ 7.66 (s, 1H), 7.60 (d, $J = 7.9$ Hz, 1H), 7.46 (d, $J = 3.6$ Hz, 1H), 7.35 (d, $J = 7.9$ Hz, 1H), 7.29 (dd, $J = 8.5$, 7.2 Hz, 2H), 7.25 (dd, $J = 8.5$, 7.3 Hz, 2H), 7.13−6.92 (m, 6H), 6.87 (d, $J = 8.9$ Hz, 2H), 4.94−4.69 (m, 4H), 4.56, (dd, $J = 10.9$, 3.9 Hz, 1H), 4.51 (d, $J = 18.1$ Hz, 1H), 4.46 (d, $J = 16.1$ Hz, 1H), 4.36 (dd, $J = 10.2$, 3.7 Hz, 1H), 4.14 (m, 3H), 3.86 (m, 1H), 1.39 (s, 3H), 1.31 (s, 3H); ^{13}C NMR (68.7 MHz, $CDCl_3$) δ 166.5, 157.9, 157.8, 138.4, 137.4, 137.3, 137.1, 130.7, 129.9, 129.6, 127.5, 121.9, 121.8, 115.1, 114.5, 114.0, 110.3, 94.8, 75.0, 74.6, 64.1, 62.9, 59.4, 55.5, 53.8, 53.3, 27.1, 26.9. Anal. ($C_{33}H_{35}IN_4O_7S_2$) C, H, N.

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Supporting Information Available: Elemental analysis. This material is available free of charge via the Internet at http://pubs.acs.org.

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